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1984 Progress Report

Center for Research for Mothers and Children

National Institute of Child Health and Human Development

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Center for Research for Mothers and Children

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INTRODUCTION

The Center for Research for Mothers and Children (CRMC) is the primary extramural program supporting research on maternal and child health at the National Institute of Child Health and Human Development (NICHD) and at the National Institutes of Health (NIH). CRMC research encompasses areas such as: fetal development, pregnancy and birth, infant mortality and morbidity, the role of nutrients and hormones in growth and development, the cause and prevention of mental retardation, and the learning and cognitive processes involved in behavioral development. Many of these research endeavors have advanced our knowledge of maternal and child development as well as directly influencing clinical practices and medical technology. To continue to meet the challenge of developing an understanding of normal and abnormal development, from conception to maturity, the CRMC stimulates fundamental and clinical biomedical and behavioral research and research training through three branches: the Clinical Nutrition and Early Development Branch, the Mental Retardation and Developmental Disabilities Branch, and the Human Learning and Behavior Branch.

The Clinical Nutrition and Early Development Branch supports research on the biological development of the fetus and infant and on the effects of genetic and perinatal conditions and events on development. Research on Sudden Infant Death Syndrome (SIDS) is of particular interest to the Branch; it is aimed at identifying the causes, mechanisms, and characteristics of infants at risk to be stricken by the syndrome. Drug metabolism and disposition studies during the pre-and postnatal periods are being conducted to gain a better understanding of drug effects during early development. The Branch also focuses on the nutritional requirements of pregnant women, the fetus and children, and on the inter-relationships among nutrition, endocrine systems, culture/behavior, and growth and development.

The Mental Retardation and Developmental Disabilities Branch supports research on the cause, prevention, diagnosis, and treatment of mental retardation and related developmental disabilities focusing on the biomedical, behavioral, and social processes that are involved. Emphasis is given to the biological bases of mental retardation (with special interest in the role of genetics) as etiological factors in such chromosomal defects as those causing Down syndrome, the Fragile X-Syndrome and the biochemical abnormalities such as galactosemia.

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The Human Learning and Behavior Branch supports animal and human research on the development of behavior, from infancy through childhood and puberty to early maturity. Studies are supported in behavioral biology; learning, cognition and preception; communication; and social and affective development.

Of special interest are prenatal and perinatal influences (including drugs and environmental agents) on infant behavior and child development. There are also initiatives on the reading disorder, dyslexia; accidents in children and adolescents; and special problems of minority children.

The research programs and staff activities of these three components of the CRMC during FY 1984 are described in detail in this report under each Branch.

HIGHLIGHTS OF CRMC RESEARCH-FY 1984

As shown in Table 1 in June of 1984, the CRMC supported 1,415 research and research training projects totaling more than $139 million dollars. This research which concerned the special health problems of children, their mothers and families comprised more than 59 percent of all the extramural funds expended by the NICHD.

Following are some highlights of research supported by the CRMC during FY 1984. These highlights are described in greater detail later in this report under each Branch.

Clinical Nutrition and Early Development Branch

Genetics and Teratology Section

- Scientists have found that a new class of extracellular proteins, soluble lectins, may participate in the organization of the extracellular matrix and influence morphogenesis by regulating cell migration and adhesion.
- Researchers are using monoclonal antibodies to study chondrogenic and myogenic cell lineages of the developing limb bud.
- Numerous studies of fetal skin development are being conducted to expand the knowledge of fetal skin's structure, function, and biochemistry.
- Scientists are studying neural crest cell differentiation in vertebrate models to better understand pluripotent cell mechanisms that give rise to a variety of cell types and tissues in the mature organisms.
- By molecular cloning of genes, scientists can continue to probe the questions of when genes are expressed and in which tissues they are active.
- Researchers are using mutant models to study limb malformations and to provide insight into normal and defective development processes.

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Table 1.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN

Funds (in thousands)

Branch/Section	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	1,415	139,609	1,256	124,740	810	88,661	371	32,997	75	3,082	113	6,818	46	8,051
Clinical Nutrition & Early Development	778	92,040	672	81,178	581	66,651	33	12,191	58	2,336	73	4,176	33	6,686
Genetics & Teratology	(348)	(37,727)	(308)	(35,207)	(266)	(31,485)	(5)	(2,277)	(37)	(1,445)	(40)	(2,520)	-	-
Pregnancy & Perinatology	(233)	(32,973)	(192)	(27,348)	(167)	(18,767)	(13)	(8,038)	(12)	(543)	(21)	(1,089)	(20)	(4,537)
Nutrition & Endocrinology	(197)	(21,340)	(172)	(18,624)	(148)	(16,399)	(15)	(1,876)	(9)	(348)	(12)	(567)	(13)	(2,149)
Mental Retardation & Developmental Disabilities	471	31,563	440	28,800	99	10,778	331	17,549	10	473	19	1,607	12	1,156
Human Learning & Behavior	166	16,006	144	14,763	130	11,232	7	3,258	7	273	21	1,034	1	209

Notes: 1) Excludes the scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included in the research projects.
3) Subprojects of program projects are counted individually in CNNE and MRDD.

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NICHD-OPE-PAS
July 18, 1984

- Scientists are using animal models to assess the extent of ultrasound-caused damage, if any, at different developmental stages and to explore ultrasound exposure-biological response relationships.

- To determine the maternal and perinatal factors contributing to disease risk, researchers are studying several neonatal infections.

- New vaccine challenge studies on cytomegalovirus (CMV) are being conducted to investigate means for preventing CMV disease in pregnant women and newborns.

- Scientists are studying the effects of maternal immunization against rubella on breast-fed newborns. Such studies will increase our understanding of infant host-pathogen interactions.

Pregnancy and Perinatology Section

- Preliminary research on insulin suggests that this hormone could play a dominant role in controlling human and sub-human primate fetal growth.

- Researchers have shown that fetuses of smoking mothers experience decreased breathing movement in the last month of pregnancy and the fetal heart rate pattern is less responsive during labor.

- By studying the metabolic effects of thyroid hormone in fetuses, scientists have shown that the hormone is not produced until either late gestation or even the early newborn period.

- Scientists have found that the release of fetal endogenous epinephrine plays an important role in the regulation of surfactant production.

- Researchers studying the rate of aquisition of cytomegaloviral infections have found that 50 percent of immune women who shed virus into breast milk and who breastfeed, transmit the infection to their offspring.

- Findings from epidemiological studies of the incidence of SIDS showed a low concordance rate in twins, irrespective of zygosity, diminishing the possibility that SIDS is of genetic origin.

Nutrition and Endocrinology Section

- Scientists have shown that 38 percent of fetuses born to zinc deficient rats develop microphthalamia (eye malformations).

- Using a sheep model that produces intrauterine growth retardation, investigators are studying the feasibility of supplemental nutritional therapy directly to the fetus. The results show that by infusing a solution of glucose and amino acids into the fetal stomach during a period of maternal dietary restriction, the birth weight and crown-rump length increases significantly when compared to unsupplemented fetuses.

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- Studies on some soy-based formulas designed for premature infants have shown that the amount of calcium ingested by the infant is quite variable.

- A team of investigators have developed behavioral paradigms to control body weight in high-risk children.

- Behavioral scientists studying anemic infants have demonstrated that infants exhibiting fearful, tense and withdrawn behavior during an evaluation show no differences during play.

- The isolation and purification of hypothalamic human growth hormone releasing hormone (GRF) has presented a major clinical research opportunity in the area of short stature. These recent advances allow researchers to distinguish the conditions of hypothalamic growth failure from hypopituitary growth failure.

- LHRH therapy has been shown to be effective in reversing the clinical features of sexual precocity in males. The LHRH pulsatile release of gonadotropins and testosterone production, retarded skeletal maturation, and slowed growth velocity.

- A sophisticated technique has been developed to measure the neurochemical and behavioral effects of local hormone infusions into the caudate nucleus of the brain of conscious rats.

Mental Retardation and Developmental Disabilities Branch

- New research studies have shown that early diagnosis and treatment of congenital hypothyroidism can prevent brain damage.

- From a mouse model that mimics the genetic abnormalities of Down syndrome, scientists have shown that a three gene sequence on mouse chromosome 16 is homologous to three of the genes assigned to human chromosome 21.

- Studies on the prenatal diagnosis of inborn errors of metabolism are being facilitated by advances in gene cloning. Successful cloning of genes will contribute to our understanding of the molecular basis of genetic disorders and their treatment.

- Researchers have found that preterm infants differ from full term infants on important behavioral measures as late as the fourth week of age.

- Scientists studying the role of early experience in the development of intelligence, have shown that exploratory behavior at 9 months of age predicts cognitive development at two years in preterm infants.

- New findings indicate that young autistic children exhibit atypical cerebral lateralization which may suggest an organic basis for autism.

- Results from an experimental exercise program for profoundly retarded adults show a decrease in self-injury and stereotyped behavior, which are persistent problems in severely retarded adults.

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- Scientists have found that Down syndrome infants and their mothers are less responsive to one another's vocalization when compared to nonretarded infants and their mothers.

Human Learning and Behavior Branch

- Studies have previously demonstrated that fetal rat pups can be classically conditioned at the 19th day of gestation. Recent evidence indicates that conditioning can occur as early as the 17th day of gestation.

- Scientists have shown that mallard duck embryos exhibit a critical period for learning of species-specific maternal call.

- Researchers have demonstrated that human newborns are responsive to classical conditioning techniques on the first day of life.

- A new technique has been developed that measures stress in neonates by quantifying the cortisol content in the baby's saliva.

- Using the reflex eyeblink augmentation, researchers have demonstrated that the hearing of one-day-old babies can be tested.

- Researchers have shown that brain sexual dimorphism exists in female rats raised in complex versus isolated environments.

- New research has shown that human infants possess intermodal perception. They can visually identify objects they had previously only felt.

- New methods that measure the characteristics of smoking behavior in adolescents have been developed.

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DIRECTOR'S OFFICE ACTIVITIES

Dr. Sumner J. Yaffe, pediatric and pharmacology clinician and scientist, continues his third year as the Director of the CRMC. During the past year, Dr. Yaffe chaired the "Symposium on Placental Transfer of Drugs," presented a paper on "Toxic Effects of Prenatally Administered Psychotropic Agents" and served as the coordinator for the Advisory Expert Panel on Pediatric Pharmacology at the XVII International Congress of Pediatrics in Manila, the Phillipines. He also gave the keynote address at the plenary session of the 5th International Society for Developmental Neuroscience, held in Chieti, Italy.

Dr. James F. Kavanagh, Associate Director of the Center, chaired a symposium and presented a paper on "Language by Ear and by Eye" in Dubrovnik, Yugoslavia. He then presented three lectures at the University of Belgrade concerning language research, the NIH and the peer review system.

Scientific staff in each of the CRMC Branches has also participated in a wide variety of research-related endeavors. These staff activities are discussed in the Branch reports which appear later.

CRMC CONFERENCES AND WORKSHOPS

To review and stimulate or to determine new directions for future research, the CRMC staff organizes and conducts workshops and conferences on a variety of different topics related to the mission of the Center. The following is a list of conferences and workshops held during FY 1984:

Conference on the Uses and Possible Abuses of Biosynthetic Human Growth Hormone
22-23 November 1983 — Baltimore, Maryland

Workshop on Sudden Infant Death Syndrome
22-24 February 1984 — Santa Monica, California

Meeting of NICHD Five Year Plan on Developmental Endocrinology and Physical Growth
5 April 1984 — Bethesda, Maryland

Workshop on In-Utero Learning
30 April-1 May 1984 — Bethesda, Maryland

Conference on Men's Transitions to Parenthood
31 May-1 June 1984 — Bethesda, Maryland

Workshop on Fetal Therapy
8 June 1984 — Washington, D.C.

Conference on Nongenetic Transmission of Intergenerational Effects of Stressors
21-22 June 1984 — Bethesda, Maryland

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Conference on Identification of Infants at Risk for Mental Retardation and Developmental Disabilities
20-22 August 1984 Bethesda, Maryland

Conference on Biobehavioral Measures of Dyslexia
10-12 September 1984 Bethesda, Maryland

Conference on The Development of Control, Coordination and Skill in the Mentally Handicapped
28-29 September 1984 Bethesda, Maryland

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Clinical Nutrition and Early Development Branch (CNED)

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OVERVIEW

The Clinical Nutrition and Early Development Branch supports basic and clinical research utilizing grant or contract mechanisms as appropriate. Training for research careers is supported through both Institutional and Individual National Research Training Awards, and also through predoctoral summer training programs and the Minority Biomedical Research Support Program administered by Division of Research Resources.

The CNED Branch contains the following three Sections:

Genetics and Teratology Section supports research into the underlying mechanisms controlling both normal and abnormal development, and is structured around the following areas: developmental genetics, developmental biology, teratology, and developmental immunology. Clinical as well as basic studies are emphasized. The goal of this program is to prevent, alleviate and treat birth defects with a special focus on the structural abnormalities.

Pregnancy and Perinatology Section supports research to advance knowledge on pregnancy and maternal health, fetal growth and maturation, and newborn well-being. Program goals take into account the interrelationships of specific health and developmental problems occurring in the prenatal, perinatal and infant periods of life, and the effects these events may have on the development and well-being of the child. Activities are organized around five maternal-infant health problem areas: high-risk pregnancy, fetal pathophysiology, premature labor and birth, disorders of the newborn, and the sudden infant death syndrome.

Nutrition and Endocrinology Section supports research and research training on the roles played by nutrients and hormones in development during fetal life, infancy, childhood, and adolescence. Program goals include the achievement of a better understanding of the relationships between nutritional and hormonal factors during normal growth and development as well as in growth retardation and developmental disorders of the endocrine system.

Table 2 summarizes the grant and contract programs for each of the three CNED Sections, giving the dollars and numbers of projects active in June 1984. Detailed reports of the accomplishments of each of the Sections are presented in the following pages.

Although total dollars in research grant support increased in FY 1984 as compared to FY 1983, the number of dollars available for research training (F-32 and T-32) decreased about 10 percent. If this trend continues, it will have significant impact on the pool of well-trained investigators in the future.

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Table 2.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
CLINICAL NUTRITION AND EARLY DEVELOPMENT BRANCH

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	778	92,040	672	81,178	581	66,651	33	12,191	58	2,336	73	4,176	33	6,686
Genetics and Teratology	348	37,727	308	35,207	266	31,485	5	2,277	37	1,445	40	2,520	-	-
Pregnancy and Perinatology	233	32,973	192	27,348	167	18,767	13	8,038	12	543	21	1,089	20	4,537
Nutrition and Endocrinology	197	21,340	172	18,624	148	16,399	15	1,876	9	348	12	567	13	2,149

Notes: 1) Excludes the scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included in the research projects.
3) Subprojects of program projects are counted individually in CNNE.

NICHD-OPE-PAS
July 18, 1984

During FY 1984, the new Small Business Innovative Research (SBIR) program was implemented. The Branch supported several of these projects for the initial Phase I or exploratory stage. At least one has proven to be sufficiently promising to move into Phase II development.

In FY 1982 the CNED Branch began an in-depth examination of research needs on intrauterine growth and fetal well-being. This emphasis has been continued in FY 1984. The papers from the FY 1983 Workshop on Intrauterine Growth Retardation were published in February, stimulating considerable interest in new research projects.

A primary thrust in FY 1984 has been the newly implemented collaborative study on control of subclinical genitourinary infections and the prevention of premature birth. This five-center project is funded jointly with the National Institute of Allergy and Infectious Diseases. After several months for protocol refinement the prospective study will commence near the end of FY 1984. NICHD also decided to expand the Perinatal Emphasis Research Centers Program (formerly MRP's) through solicitation for a new center on perinatal pharmacology and one on intrauterine growth retardation. An NIH/NICHD consensus development conference on the use of diagnostic ultrasound helped to clarify the value and appropriateness of this technique for fetal assessment early in pregnancy. Additional studies on the safety of ultrasound and the long-term consequences for the offspring are being solicited.

Parallel with the increased attention being given to the problem of high risk pregnancy and IUGR, the Branch is experiencing a significant upsurge in applications on genetics and underlying processes. Thus the Genetics and Teratology Section of the Branch has grown rapidly. Several conferences and contract efforts are under development for early FY 1985. Similarly burgeoning interest in endocrine control of growth and physiologic development has prompted the appointment of an expert panel to recommend the most promising research areas for emphasis in the years ahead.

Branch staff are frequently called upon to serve on a wide range of task forces and work groups involving other Institutes of NIH, federal agencies, and professional organizations. These reflect the professional recognition of the staff by their peers and colleagues. Details of these activities are given in the following Section reports. In addition to these activities, the chief of the Branch, Dr. Merrill S. Read, currently serves as NIH representative to the DHHS Task Force on Maternal and Infant Nutrition and to the USDA/DHHS Nutrition Education Committee for Maternal and Child Health Publications. He represents NICHD on the Executive Committee of the USDA-Baylor Children's Nutrition Research Center in Houston. Currently he is completing his third year on the Governing Council of the American Public Health Association and also is on the Committee on Nutrition in Medical Education of the NAS/NRC. Finally, Dr. Read serves as Chairman of the Committee on Education and Training of the American Society for Clinical Nutrition.

During the summer of 1984, the Branch benefited greatly from the services of four summer students. These students contributed significantly to the Branch's efforts to streamline and improve the scientific management information systems as well as assisting in a wide range of other Branch activities.

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David Griver, a medical student at Howard University, worked with the Genetics and Teratology Section staff to document information on specific human teratogens. Mr. Griver also devised a system of key words which are now being evaluated for compatibility with the NIH data base. This system would enable Branch staff to obtain information more efficiently from the NIH-wide system.

Another medical student from Howard University, Dyrel Bartee, worked with the Branch staff to update and computerize selected information from grant files and assisted in preparing the section report to the National Advisory Child Health and Human Development Council. Mr. Bartee also began preliminary planning and organization of the maternal hypovolemia project.

A senior at Yale University, Margaret L. Baer, made a long-lasting contribution to the Nutrition and Endocrinology Section by creating a sophisticated computer program, complete with a 54-page instruction manual. The program enables the staff to monitor the progress of grants and contracts and to identify significant research accomplishments. Ms. Baer's program not only met the Section's needs, but will also serve as a prototype for other components of NIH.

Yula Ponticas, a graduate student at the University of Florida, Tallahassee, worked with the Nutrition and Endocrinology Section to abstract approximately 70 progress reports from on-going grants and contracts for incorporation into the scientific information system. Ms. Ponticas also organized and edited the proceedings of a Section-sponsored conference on human milk banking.

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Genetics and Teratology Section

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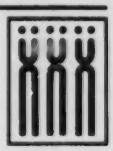

PROGRAM ACTIVITIES

The research program of the Genetics and Teratology Section (CNGT) is built on the premise that events very early in life can contribute to the life-long health and well-being of children and adults. This view avows that human development is a continuous process that begins with the maturation of male and female germ cells, is followed by fertilization, and continues through embryonic, fetal and childhood development until full adult maturation is reached. It also stresses that maximum adult potential cannot be reached if there are serious deviations from the normal developmental program.

Developmental defects afflict 3 to 7 percent of all babies born each year. The physical and mental disabilities these defects constitute can pose life-long suffering and morbidity for the affected individuals. Developmental errors are also the cause of one death in five of all infants who die by the age of four years. Other developmental errors manifest themselves at much earlier maturational stages as a major proportion of spontaneously miscarried pregnancies.

Most developmental defects are initiated during early developmental phases, some as early as gametogenesis. For this reason, the CNGT research program places an ever increasing focus on studies of early embryo development with the aim of identifying not only the early stages at which defects may be triggered, but also the etiologies and mechanisms through which defects are produced. Various causes of congenital defects are studied by NICHD-supported investigators: gene mutations, chromosomal aberrations, embryo-intrinsic and environmental agents, maternal metabolic imbalances, multifactorial etiologies and those of unknown origin. Mechanisms at the gene, chromosome, cell and tissue levels are studied using new technologies such as improved cell cultures, recombinant DNA and monoclonal antibodies, to better integrate basic biological and clinical investigations. New epidemiological models allowing more sophisticated data analysis are also employed.

Among the congenital defects, those of a structural nature represent research emphasis areas of the Section. Studies of early embryo development, normal and abnormal limb development and both normal and abnormal skin morphogenesis are highlighted for increased attention. Genetic and biological aspects are supported as well as teratological, clinical and epidemiological investigations of all malformations. The Section also fosters a research program on maturation of the immune system that includes adverse pregnancy and early postnatal outcome produced as a result of immunologic responses or immaturity of the defense system.

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EMPHASIS AREAS

The Genetics and Teratology Section has been divided into four component research areas which complement each other, but which also contain some overlap so that the various activities must be viewed together as an overall effort. These areas comprise:

1. Developmental Biolcgy to determine the mechanisms underlying normal human development against which aberrations of the process can be understood.
2. Developmental Genetics to determine the hereditary influences underlying developmental disorders and to understand hereditary instructions for the developmental process.
3. Teratology to assess adverse genetic and/or environmental influences on development, and to arrive at mechanisms by which developmental aberrations are produced.
4. Developmental Immunology to understand maturation of the immune system as well as adverse pregnancy and early postnatal outcome produced by immunologic responses or immaturity of the defense system.

FINANCIAL SUPPORT

As of June, 1984, the Genetics and Teratology Section funded a total of 348 projects at the level of $37,727,000 (Table 2a). Over the last year there was an increase in support by all funding mechanisms for both research and training within this Section. By far the greatest increase was in the number of research projects (ROIs) funded; this represents 35 additional research projects at a cost of $6,543,000 during FY 1984. Because of new technology, especially recombinant DNA methodology, we anticipate an opportunity to foster even stronger programs of research in developmental biology and plan to focus concerted efforts on studies of early embryonal development.

RESEARCH TRAINING

The Genetics and Teratology Section provides training support through two funding mechanisms: (1) National Research Service Awards granted to institutions for support of both pre-doctoral and post-doctoral research trainees elected by those institutions (T32s and T35s); and (2) National Research Service Awards granted to individual post-doctoral fellows seeking full-time research training with a trainer of their choice (F32s and F33s). During June 1984, the Section funded 21 institutional training awards and 19 individual training awards. The largest portion of the training support is in the area of developmental biology.

CONTRACT PROGRAM

The Section provided no contract support in FY 1984. However, several contracts are currently being developed that are intended to provide research resources for Section-supported research projects. Two contracts are targeted for award early next fiscal year: an animal model of neural tube defects and a banking facility of monoclonal antibodies to be made available to NICHD-supported investigators of early embryonal development and limb development. A third contract effort is planned to support a human DNA probe repository.

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Table 2a.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
GENETICS AND TERATOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	348	$37,727	308	$35,207	266	$31,485	5	$2,277	37	$1,445	40	$2,520	-	-
Clinical Genetics	25	3,677	24	3,659	18	2,534	2	992	4	132	1	18	-	-
Basic Developmental Genetics	76	7,450	68	7,220	51	6,114	1	479	16	628	8	230	-	-
Early Embryonic Development	108	11,597	89	9,946	76	9,023	1	449	12	474	19	1,651	-	-
CNS Development	21	2,017	18	1,964	17	1,923	-	-	1	41	3	53	-	-
Limb Bud Development	6	426	4	389	4	389	-	-	-	-	2	37	-	-
Chondrogenesis	8	963	8	963	8	963	-	-	-	-	-	-	-	-
Myogenesis	19	2,056	18	2,038	16	1,956	-	-	2	82	1	18	-	-
Teratology-Biological Causes	10	1,598	8	1,332	8	1,332	-	-	-	-	2	266	-	-
Teratology-Physical & Chemical Causes	18	1,942	17	1,901	17	1,901	-	-	-	-	1	41	-	-
Ontogeny of Immunity	21	2,031	19	1,871	17	1,784	-	-	2	88	2	159	-	-
Neonatal Infection	14	1,552	13	1,506	12	1,150	1	357	-	-	1	46	-	-
Immunology of Breast Milk	7	636	7	636	7	636	-	-	-	-	-	-	-	-
Reproductive Immunology	15	1,780	15	1,780	15	1,780	-	-	-	-	-	-	-	-

Notes: 1) Excludes the scientific evaluation grants.
2) The Minority Biomedical Support grants (S06) are included in the research projects.

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RESEARCH HIGHLIGHTS

DEVELOPMENTAL BIOLOGY

Cell Recognition: Interactions that occur at the cell surface apparently modulate the behavior of cells during embryogenesis. Important morphogenetic behaviors, for example, cell proliferation, cell adhesion and cell movement, yield the organized three-dimensional form of the embryo. Errors in these cellular behaviors could result in congenital malformations or even death of the embryo. Two groups of molecules are likely to have a role in providing the specific information for normal morphogenesis. These are glycoproteins and lectins.

One NICHD-supported research group studies the synthesis and function of glycoproteins during embryonic development. Until now their research focused almost exclusively on the sea urchin embryo and provided strong evidence that glycoproteins are involved in gastrulation. They showed that the mRNAs for these glycoproteins were localized to the membranes of the unfertilized egg, or the pregastrulation embryo or the gastrula stage embryo, indicating that different modes of regulation are used during gastrulation. Based on the strength of this and other evidence, these researchers are now using the mouse embryo to study the biosynthesis of glycoproteins, looking for stage and tissue specific differences which might suggest functional roles for glycoproteins. Study of mouse mutants which develop abnormally will look for a link between glycoprotein synthesis and birth defects.

The second group of molecules, the lectins, interact with glycoconjugate ligands, including glycoproteins. They are isolated from many organisms and are subdivided according to being integrated into membranes or being soluble at extracellular sites. Soluble lectins appear to play a role in tissue differentiation, as suggested by their striking developmental regulation in Dictyostelium (slime mold) and in vertebrate tissues. A large research group which has concentrated on lectin synthesis and function for many years is now stressing studies of soluble lectins. They have discovered and purified several lectins in vertebrates and the slime mold, have raised specific polyclonal antisera to the lectins, and have used them: 1) to localize the lectins in specific tissues; 2) to show that two lectins were expressed differently during development; and 3) to show that only 1-2 percent of total cellular lectin was present on the cell surface. Now they are determining the glycoprotein ligands for each lectin. Since lectin-ligand interactions occur both in the extracellular matrix between cells and in materials coating tissue surfaces, this work on glycoproteins and lectins should have bearing on a variety of medical problems, especially on understanding the etiologies of certain developmental malformations.

Extracellular Matrix: While the extracellular matrix (ECM) was cited above as the location of some soluble lectins, it is actually a compartment of many more substances which influence the growth and differentiation of groups of cells. At least a dozen NICHD-supported laboratories are exploring the composition and function of the ECM. It is hoped that knowledge of the cellular mechanisms responsible for embryonic organ formation will lead to an understanding of the etiology of malformations and ultimately to their prevention.

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A cell that possesses a particular group of substances on its surface will interact with its neighbors and with the ECM in such a way as to migrate in a certain direction and stop at a certain place. The role that ECM materials play in the processes of tissue interactions is being studied in many systems: cultured cells, sea urchin, chick, mouse and rat, and there has been considerable progress on several projects. The potential clinical relevance of studies on the ECM is most apparent in the work of one group which focuses on remodeling of the ECM during morphogenesis. Persistent pulmonary hypertension of the newborn is associated with both prenatal hypoxia and increased pulmonary arterial smooth muscle mass. They showed that the hypoxia does not act directly on smooth muscle cells from the pulmonary artery. Instead, they concluded that heparin, an ECM component, inhibits proliferation of expanding, as well as quiescent, muscle cells. They suggested that heparin-like molecules, which are ubiquitous on cell surfaces, may be regulators of these muscle changes in the perinatal period.

Limb Development: Studies of the developing limb attempt to establish chrondrodrogenic and myogenic cell lineages by using monoclonal antibodies which have been prepared to cell surface antigens of different limb cell populations. Antigens which specifically recognize myoblasts and myotubes can now be used to trace the myogenic cell lineage. Other antibodies are being prepared to identify chondrogenic cell populations and then to study tissue interactions that are necessary for chondrogenesis to occur. The developmental transition to fully differentiated chondrocytes is further studied at the gene level. Messenger RNAs prepared from prechondrogenic mesenchymal and fully differentiated chondrocyte cell populations were used to construct cDNA probes. These probes are used to investigate the regulatory mechanisms of different collagen molecules that characterize the chrondrogenic transition. The information obtained from these studies is important since malfunctions of the genes and gene products that characterize chondrogenesis undoubtedly contribute to the skeletal defects which occur during embryonic development and are expressed in many recognized genetic diseases.

Skin Development: Scientists in specific areas of skin biology are working together to learn more about normal and abnormal fetal skin development. It is now known that the skin of the human embryo forms a simple epithelium soon after conception and that the epidermis and dermis are established in the second week of embryonic life. From this time on these layers develop at different rates but the epidermis reaches its definitive state more rapidly. The epidermis is keratinized and the stratified squamous epithelium as well as all the adnexal structures are formed by the end of the second trimester. At this stage, the dermis is less than half its full thickness as compared to adult skin. However, skin development is never complete since the epidermis turns over continually and remodelling of the dermis continues throughout life. These multidisciplinary studies will continue to explore the structural, biochemical and functional properties of developing human skin including quantitation of hemidesmosomes at the dermal-epidermal junction, studies of epidermal proteins, specific classes of lipids, interstitial collagens, glycosaminoglycans and collagenase of the dermis, and evaluation of transport across the epidermis. Further studies of fetal skin structure should lead to an integrated understanding of fetal skin biology. These studies have special importance since fetal skin is one source of the amniotic fluid cells used in the prenatal diagnosis of certain metabolic diseases and biopsies of fetal skin are used to diagnose others.

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CNS Development: Studies of central nervous system development include the differentiation of the vertebrate neural crest, which gives rise to an amazing variety of cell types and tissues in the mature organism: sensory and autonomic neurons, nerve supporting cells, pigment cells, and endocrine cells. In cranial regions, neural crest cells also give rise to muscle, skin and bone. NICHD-supported investigators have developed neural crest cell culture systems to study crest differentiation and specialization into different kinds of crest-derived tissue under precisely controlled experimental conditions. They showed that cloned, early crest cells, at the onset of migration, are capable of giving rise to both neurons and pigment cells. Certain environmental conditions changed the commitment of neural crest cells from presumptive neurons to pigment cells. Also, pigment cells can undergo terminal differentiation early in embryonic development whereas future neurons must undergo additional cycles of cell division before they can differentiate. These studies enable a major advancement in understanding the regulation of normal neural crest differentiation and the cellular defects that result in crest-derived birth defects and disease.

DEVELOPMENTAL GENETICS

Understanding the basis for congenital malformations requires that one knows how the gene products responsible for embryogenesis are regulated. Several new research approaches being used by NICHD-supported investigators promise to advance our understanding of early developmental genetics. The well-established techniques of molecular genetics have led to new data in old systems and to development of new experimental approaches. The bithorax complex of developmental mutants in the fruit fly, Drosophila, have been studied for some 30 years, such projects being part of NICHD much of that time. These studies provided a strong descriptive, biological and classical genetic background of information about these complexes. Mutants in these gene complexes were used to show that master regulatory genes were probably responsible for controlling the differentiation of primitive body segments into head, thoracic and abdominal segments with the appropriate appendages. Just recently these mutants, and the cloned DNA gene sequences responsible for the defect, have been used to show that there is a particular DNA sequence which regulates this complex, and that this same sequence can be found in the DNA of vertebrates, including mice and man. This "homeo box," as it is called, will be studied further to learn its evolutionary and developmental significance.

Molecular cloning of other genes, especially in simpler organisms, is allowing other NICHD investigators to study when different cells in a developing organism turn a gene on or off. They have found that gene "families" exist. This refers to the occurrence of several genes which result in the same or similar forms of a protein, but which are expressed differently. Thus, one gene may be active earlier than the related gene, or in a different tissue type. Each gene family probably has a distinct pattern of expression regulated in a specific manner. Considerable effort is now being made to gather and compare this new information, searching for general principles of gene regulation.

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How nuclear genes become restricted during development and how the cytoplasm affects the nucleus and contributes to development of the mouse is being studied by one group through transplantation of nuclei from embryonic cells into a recipient ovum. They found that although older nuclei can be transferred, the embryos do not develop. This contrasts with results on amphibians, and suggests that mammalian nuclei become "restricted" early and are not "reprogrammable." This procedure is also used to do reciprocal pronuclear transplantations between genetically distinct one-celled embryos. The experimental goal is to define the degree to which maternally-inherited cytoplasmic components persist as development progresses. Lastly, this technique has been used to construct diploid mouse embryos with two female pronuclei or with two male pronuclei. They found that these embryos do not develop to term and they concluded that the maternal and paternal contributions to the embryonic genome in mammals are not equivalent and the combination cannot support complete embryogenesis.

TERATOLOGY

Studies in teratology approach an understanding of the causes of human developmental defects. Epidemiological investigations look for a relationship between possible causative factors and adverse pregnancy outcome. Animals and cell cultures are used to study the teratologic targets and determine the affected developmental reactions which produce birth defects. Other studies employ teratogens to establish the role of various cellular components and biological organizations in the developmental process. The progress for several representative teratological investigations follows below.

Epidemiology of Birth Defects: Epidemiological studies combined with cytogenetic and pathological approaches are done to examine a variety of adverse exposures during pregnancy, including fever, spermicide usage, drinking of alcohol and the consumption of various caffeine-containing beverages. An analysis of the effects of smoking found a strong association of smoking with trisomic pregnancy loss preferentially in older women, while trisomic abortions in younger women were less likely to occur as a result of smoking compared to normal controls. Since this effect varies with maternal age, the investigators suggest that the causes of recognized trisomic abortions differ in younger and older women. Studies of this nature will develop a deeper understanding of the etiologies of congenital abnormalities and will provide a basis for more precise reproductive counseling.

Limb Malformations: The new focus in this Section on studies of developmentally-caused limb malformations will attempt to elucidate the various etiologies and the affected developmental processes through which these defects are produced. Investigations center on the causes of abnormal development of cartilage, muscle and bone. Progress has been made in the study of the production of defective cartilage by various mutations that cause abnormal biosynthesis of major cartilage extracellular matrix components. The synthesis of cartilage matrix proteoglycans is altered by mutations at several steps. Nanomalia (in the chicken) and cartilage matrix deficiency (in the mouse) produce changes in the synthesis of proteoglycan core proteins. Chondrodystrophy (in the turkey) alters the glycosylation of the proteoglycan core proteins. And brachymorphy (in the mouse) affects the sulfation of component glycoseaminoglycans to yield defective

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proteoglycan monomer molecules. Use of mutants in these studies not only gives insight into some defects underlying limb deformities but also aids in the identification of normal developmental processes that are essential for normal limb maturation.

Bioeffects of Ultrasound: The benefits from the diagnostic use of ultrasound in obstetrics are now widely recognized and appreciated, and the technology is accepted as an indispensible prenatal diagnostic tool. However, the potential risks from ultrasound exposure to the developing fetus have not yet been adequately investigated. Therefore, this Section is developing a new research emphasis that will include clinical studies on the prenatal use of ultrasound and laboratory investigations at the cellular and animal level, both intended to provide indications of possible adverse biological effects in humans. One NICHD-supported investigation utilizes the rat model to assess ultrasound-caused damage at different developmental times looking for postnatal neurological, cardiovascular and excretory system effects. It also investigates the thermal, cavitational or mechanical mechanisms by which abnormal development of organisms may be produced. These data should allow better definition of the ultrasound conditions under which developmental defects may or may not be initiated.

DEVELOPMENTAL IMMUNOLOGY

Studies on the ontogeny of immunity are pursued to better understand interactions of the immune system at humoral and cellular levels during embryonic stages of development and on through fetal, newborn, infant and adult life. Immunologic deficiencies resulting from aberrations in this developmental continuum require a great diversity of research approaches.

The Complement System: One group of scientists is supported by NICHD to study defects in the complement system which consists of 20 specific plasma proteins. The defects result in increased susceptibility to "autoimmune" disease or to infections by certain bacteria. Certain components of the complement system have been identified which, when deficient, result in specific clinical pathologic conditions. Complement assays for these components are now used as an aid in diagnosis. These assays, as well as dysfunctional proteins found in some patients, have led to interest in genetic heterogeneity in these deficiency states. Exciting new studies have been designed to provide a molecular analysis of structure, organization and polymorphisms of genes within the major histocompatibility complex and to attempt to define predictive independent markers for these disorders. Fetal liver produces complement components in vitro, but this ability may be limited in the newborn period either due to increased metabolism or to decreased production, resulting in reduced serum levels. Studies are underway to better understand the control of complement production. When type specific antibody is not available, the newborn must rely on the alternative complement pathway to destroy microorganisms. Studies are exploring the means to increase alternative complement pathway activation. This may lead to a pharmacologic means to improve the newborn's ability to initiate an immune response to microorganisms protected by a capsule rich in sialic acid and for which no type specific antibody is available.

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Neonatal Infections: Understanding of the physiological, immunological and pharmacological uniqueness of the newborn and infant has led to improved prevention and treatment of infectious diseases in this age group. In addition, considerable research effort has been applied to studies of Group B streptococcus, pneumococcus, gram-negative rod and cytomegalovirus infections to better understand responses to specific microorganisms. Examples of these studies follow.

Over the past two decades Group B streptococcus (GBS) has been a predominate cause of perinatal infections in the United States with an estimated incidence of 2-3/1,000 live births. Of special importance are the early forms of infection, and currently funded NICHD investigators focus on maternal/perinatal factors contributing to disease risk. This is being achieved through studies of the natural history of these infections, through serotyping investigations in pregnant women, newborns and infants, and through clinical, bacterial and immunologic evaluations in order to critically define contributing factors to the disease state. Current evidence indicates that GBS vaccine or intravenous immunoglobin may enhance neonatal immunity. Antibiotic therapy of pregnant women colonized with this organism appears to prevent neonatal and maternal GBS disease. However the use of routine penicillin prophylaxis, even when administered less than one hour after birth, remains questionable for its safety as well as its effectiveness. There is concern both for development of penicillin-resistant pathogens and penicillin allergy. In addition, there is concern that routine single injections of penicillin may not be effective treatment and may allow the disease to progress without being diagnosed.

Current data from NICHD-supported researchers indicate that about 1 percent of all infants are infected with cytomegalovirus (CMV) in utero, of which 15-25 percent will have damage to the central nervous system such as mental retardation, psychomotor problems or hearing defects. This could be prevented by availability of an effective and safe means of providing CMV vaccination for women prior to pregnancy. Important new vaccine challenge studies are now being carried out on immunologically normal male individuals to determine the efficacy of a vaccine. These investigations are directed toward an effective immunologic strategy with special emphasis on prevention of CMV disease in pregnant women and newborns.

Other NICHD-supported studies have evaluated the effect of maternal immunization against rubella in the immediate postpartum period on lactation products. These studies provide clear evidence for the excretion of rubella virus in breast milk after maternal post partum immunization with live, attenuated rubella virus vaccine. None of the infants developed clinical disease attributable to rubella virus during a 20 week follow-up. But the development of a transient immunologic response in some and lack of immunologic response in other infants harboring the virus indicate host-pathogen interactions in the neonatal period that differ and require further investigation.

STAFF ACTIVITIES

Recently several newly targeted research areas have been encouraged to meet more specific goals of the Genetics and Teratology Section. These include: 1) Normal and Abnormal Limb Development - An NICHD workshop on "Normal and Abnormal

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Development of the Limb" resulted in specific research recommendations. The proceedings of this meeting were published (Krey et al., Teratology 29: 315-323, 1984). Staff has now developed a "Request for Applications" (RFA) and presented it to the scientific community to foster additional research efforts in studies of limb development. 2) Developmental Studies of Fetal Skin - A workshop entitled "Morphogenesis and Malformations of Skin" was organized by Mrs. Anne Krey, CNGT staff, and was held in September, 1983, with a focus on fetal skin development. Skin is considered a neglected organ system and studies of its function during normal development as well as in disease states with emphasis on in utero development will be further encouraged by Section staff. Mrs. Anne Krey also participates in an Ad hoc Interagency Dermatology Working Group which fosters this research area. 3) Bioeffects of Ultrasound - NICHD took the lead in organizing a Consensus Development Conference on "The Use of Diagnostic Ultrasound Imaging in Pregnancy" which took place in February, 1984. CNGT staff maintained close contact with these activities throughout all stages of organization. In addition, Dr. Delbert Dayton, Section Chief, and Mrs. Anne Krey, CNGT staff, represent NICHD on the Public Health Service Steering Committee on the Bioeffects of Ultrasound. This committee was organized in response to the request of the Assistant Secretary for Health to assess the needs for further research and to recommend a potential research agenda. Dr. Dayton was appointed chairperson of a subcommittee which organized a workshop entitled, "Bioeffects of Ultrasound on the Developing Organism," and Mrs. Krey served with him in that activity. The recommendations from this workshop and deliberations of the steering committee have been developed into a report which is nearing completion. CNGT staff are now planning a "Request for Applications" to stimulate further research in ultrasound bioeffects. 4) Studies of Early Embryo Development - Dr. Jeanette Felix, expert consultant to CNGT, is working with staff to expand studies of early embryonic development as a research priority area. The entire research program is being reviewed and a conference is being planned for the next fiscal year on "Genetics of Early Mammalian Embryogenesis." 5) Developmental Neurobiology - Mrs. Anne Krey, working closely with NICHD intramural staff, is planning a conference for February, 1985 on "Molecular and Developmental Neurobiology."

In addition, Dr. Dayton is a member of the NIH Coordinating Committee For Blood and Its Substitutes established by the Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Resources. He has also been appointed to the NIH Cystic Fibrosis Coordinating Committee which functions to stimulate and plan for research activities across NIH. Dr. Dayton represents NICHD on the NIH Working Group for Reye Syndrome which facilitates coordination of research efforts on this important health problem of children. A jointly sponsored NIH Announcement has been published and has been helpful in developing new research applications to strengthen efforts to study this disease. In addition Dr. Dayton serves as a member of the Public Health Service Reye Syndrome Task Force which has developed a protocol for a case-control study of the association between Reye Syndrome and salicylate intake. A pilot study has just been completed and data are being analyzed. The definitive study is planned to begin in December, 1984 through the assistance of State Health Departments. Dr. Dayton has recently been appointed to the Interagency Risk Management Council (IRMC) Working Group on Reproductive Effects. The Environmental Protection Agency has the lead in this activity and the working group is to promote interagency cooperation in the assessment of risks to human reproduction and to development of the human conceptus in the field of reproductive toxicology.

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Pregnancy and Perinatology Section

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PROGRAM ACTIVITIES

EMPHASIS AREAS

Activities of the Pregnancy and Perinatology Section are organized around five maternal-infant emphasis areas.

1. High Risk Pregnancies: Over the last 20 years significant progress has occurred in maternal survival and well-being which has surpassed improvements in fetal outcome. Research efforts on high risk pregnancy are directed towards the closure of this gap while continuing studies in both normal and abnormal pregnancies.

2. Fetal Pathophysiology: Studies in fetal pathophysiology are examining the factors influencing normal and abnormal embryonic development. Efforts focus on normal and abnormal development at the molecular, tissue, and organ levels. Emphasis is placed on studies facilitating the assessment of fetal status to provide meaningful antenatal diagnosis. Another area of special interest examines the mechanisms responsible for intrauterine growth retardation and its consequent increased morbidity and mortality.

3. Premature Birth and Labor: Premature labor and birth is a major cause of neonatal mortality and morbidity. Two-thirds of all infant mortality occurs among infants weighing 2500 grams or less at birth. Furthermore, the nation's high prematurity rate is responsible for our relatively poor performance in infant mortality compared to other countries. Consequently, this program supports studies of the normal onset of labor, why labor sometimes begins prematurely, and how premature labor might be stopped without detrimental effects.

4. Disorders of the Newborn: Disorders of the newborn are responsible for approximately three-fourths of the infant deaths in the United States, and produce long-term disability for many individuals who are affected by them and survive. Research directed toward reducing the impact of these disorders includes studies of maternal health problems that affect the status of the infant, adaptation of the newborn infant to its environment, and problems in the early weeks of life that influence subsequent development and behavior.

5. The Sudden Infant Death Syndrome: The NICHD has made particular efforts to encourage research on the sudden infant death syndrome (SIDS) since 1974. Research to date has demonstrated that the SIDS infant no longer can be viewed as having been perfectly healthy prior to death, but rather is believed to have

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Table 2b.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
PREGNANCY AND PERINATOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	233	$32,973	192	$27,348	167	$18,767	13	$8,038	12	$543	21	$1,089	20	$4,537
High-Risk Pregnancy	81	11,432	68	9,688	61	6,314	5	3,272	2	102	5	253	8	1,491
Fetal Pathophysiology	54	7,416	49	6,898	41	4,791	3	1,886	5	221	2	111	3	407
Premature Labor and Birth	38	6,512	31	4,467	29	3,313	2	1,153	-	-	2	36	5	2,009
Disorders of the Newborn	47	6,039	34	5,181	28	3,326	3	1,727	3	129	12	689	1	169
Sudden Infant Death Syndrome	13	1,575	10	1,114	8	1,023	-	-	2	90	-	-	3	461

Note: The Minority Biomedical Support grants (S06) are included in the research projects.

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had developmental abnormalities. Current research efforts are directed towards identifying the cause(s) of SIDS, and improving methods for helping families cope with a SIDS death.

PERINATAL EMPHASIS RESEARCH CENTERS - (PERCs)

As a focal adjunct to research projects in the above five areas, NICHD has established in 1977 Major Research Programs (MRP's) to provide an integrated approach to major unresolved problems in perinatal medicine. The official designation of the MRP's was changed to PERC during FY 1984 in order to provide consistency in nomenclature for all Research Center programs at NICHD. PERC's support multidisciplinary research in areas where knowledge gaps have not been sufficiently addressed by ongoing research or where promising areas are in need of special stimulation. The Section supports six PERC's; four are in the area of diabetic pregnancies, one in prematurity, and one in fetal hypoxia. Requests for Applications have been published for two new Centers, one in the area of perinatal pharmacology and toxicology and the other addressing causes, mechanisms and consequences of intrauterine growth retardation.

FINANCIAL SUPPORT

As seen in Table 2b, the Pregnancy and Perinatology Section supported 215 research grants and contracts during FY 1984 amounting to $27.3 million. The Section holdings amounted to approximately 21.8 percent of the research grants, 56.3 percent of the research contracts and 16 percent of the research training supported by the Center for Research for Mothers and Children.

RESEARCH TRAINING

During FY 1984, the Section supported a modest amount of research training, provided through two types of grants: Individual Postdoctoral Fellowships (F32's, F33's, F34's) and Institutional Research Training Grants (T32's). The twelve institutional (T32) grants supported 48 trainees (6 predoctoral, 42 postdoctoral), a majority in Departments of Pediatrics (8), 3 located in Departments of Obstetrics, and 1 in a non-clinical department. One was in the area of high risk pregnancy, another one in fetal pathophysiology, and 10 in the various aspects of perinatal medicine which include disorders of the newborn. Eight Individual Postdoctoral Fellowships (F32's) were funded in FY 1984.

The Section also supported 13 Research Career Programs, 4 under Special Emphasis Research Career Award (K01, SERCA), 7 under the Modified Research Career Development Award (K04), and 2 under the Clinical Investigator Award (K08). The majority of these (69 percent) were in a Department of Pediatrics.

CONTRACT PROGRAM

The Section's contract program complements the grant program and meets special needs in perinatal research.

In 1969, NICHD recognized a growing awareness of the potential for non-human primates in perinatal and developmental research. A special breeding colony was established in 1971 under contract at Davis, California to provide rhesus

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monkeys of known medical, reproductive and geneological history to NICHD-supported investigators in the United States.

NICHD in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) awarded six contracts in FY 1984 (5 clinical centers [NICHD] and 1 data management center [NIAID]) to carry out a clinical trial, entitled "Prevention of Prematurity by Detection and Treatment of Gestational Genitourinary Infections: A Multicenter Randomized Controlled Clinical Trial." The objectives of these contracts are to identify specific types of maternal genitourinary infection which are significantly associated with preterm labor and birth, and to test whether appropriate antimicrobial therapy of such infections can reduce the preterm birth rate in women at risk.

RESEARCH HIGHLIGHTS

RESEARCH ACCOMPLISHMENTS OF THE PERCs

Four PERCs are in the area of "Diabetic Pregnancy," a major problem for mothers and children. Untreated diabetes mellitus is incompatible with successful outcome of pregnancy. As treatment of diabetes has improved, pregnancy outcome has improved, and presently maternal mortality is similar for both diabetic and nondiabetic women. However, maternal morbidity continues to be higher in diabetics. Fetal mortality has been reduced but not to the level in the general population. Increased incidences of congenital anomalies, macrosomia, late intrauterine death, and respiratory distress syndrome (RDS) remain a significant problem. Pregnancy per se has a diabetogenic effect, and some women develop abnormalities of carbohydrate metabolism known as gestational diabetes mellitus (GDM).

Animal models (rhesus monkey, rat, lamb) have been developed to produce chronic in utero hyperinsulinemia resulting in fetal overgrowth (similar to human fetal macrosomia). Researchers have shown that insulin appears to play a predominant role in controlling human and subhuman primate fetal growth. Measurements of fetal somatomedin in humans support this concept as no differences were found between the levels in insulin-dependent diabetics (IDD) and in non-diabetic controls. Fetal macrosomia was also produced in rats by injecting insulin directly into the fetus, which indicates that insulin is a lipogenic hormone. Another approach to produce fetal hyperinsulinemic state is to induce diabetes in the pregnant rat by the administration of streptozotocin in early gestation. Investigators showed that even though the maternal diabetes is corrected with insulin therapy, the fetal abnormalities are rectified only partially. In addition, it was demonstrated that the observed increase in placental size is related to maternal glucose levels rather than to fetal insulin concentrations. One of the centers has successfully established and standardized a whole rat embryo culture system which will provide the means to study events occurring in a high glucose environment and characterize their effect upon growth and maturation. Studies using cultured isolated islets from the pancreas of fetal rats have shown that insulin release, both at basal and stimulated conditions, is greater in islets obtained from normal fetuses than in those whose mothers were treated with streptozotocin. The latter islets showed extensive disorganization and with the use of specific staining techniques they exhibited minimal staining for insulin and no changes for glucagon.

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Studies in humans examining fuel metabolism in non-gravid, third trimester pregnant women with normal carbohydrate metabolism and in the well-controlled insulin dependent diabetic patient are providing the rationale for the desirability of multiple feedings in the management of the pregnant diabetic and highlight potential harms of even mild caloric restriction. Pregnant women who had a diagnosis of GDM early in pregnancy are more likely to have postpartum glucose intolerance indicating that the time of detection of GDM, diagnosed by an abnormal oral glucose tolerance test, may have prognostic significance.

One of the centers has developed a small, subcutaneously implanted intraperitoneal access device for use in insulin resistant diabetic patients and they are beginning to test it in animals. Simultaneously they are progressing in the development of an external programmable microelectronic control system for the regulation of the infusion of insulin in ambulatory patients. Eventually this system is to be used together with an implantable pump and reservoir for insulin administration after appropriate programs are developed. These technical advances would facilitate the treatment of insulin-dependent diabetic pregnant women and children.

Cigarette smoking is recognized as a health hazard which extends to fetuses of smoking pregnant women. Adverse effects on pregnancy range from increased risk for reproductive loss, fetal mortality, preterm birth, and neonatal death, to retardation in fetal growth as reflected in birth measurements of lower mean body weight, shortened body length, and smaller head circumference, as well as to a number of problems of adaptation in the neonatal period. In addition, there is suggestive evidence of long-term impairments in physical growth, diminished intellectual function, and deficiencies in behavioral development for those babies who survive the first four weeks of life. Investigators at one of the PERCs are systematically examining fetal changes occurring as a consequence of maternal smoking during human pregnancies as well as in animal models. Fetuses of smoking mothers show a decrease in fetal breathing when studied in the last month of pregnancy and a heart rate pattern less responsive during labor. These findings may reflect a difference in the control of respiratory and cardiac functions related to maternal smoking.

A prospective study of smoking mothers and their controls has shown that, as expected, the birth weights of the "smoking-exposed" infants were decreased. Using a rat model for maternal smoking, it was determined that fetal growth retardation is not solely the result of reduced caloric intake by the mother, and that fetal lung growth is inhibited in greater proportion than other organs. Examination of human placentas from smoking mothers reveals an increase in total cell number and decrease in mean cell size, which is compatible with a hypoxic or toxic insult followed by an adaptive response.

Prematurity is associated with more than 60 percent of all infant deaths and increased morbidity in the survivors. In general, the premature, and therefore immature infant has a greater possibility of exhibiting intellectual and other neurologic deficits.

One center is actively pursuing studies to clarify the mechanisms implicated in the initiation of parturition in order to prevent premature birth. The investigators are focusing on a series of biochemical events that accompany the onset of

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labor, to define the metabolic communication system in the human fetus, amniotic fluid, fetal membranes, and decidua vera and are trying to identify the fetal maturational processes that initiate parturition. It has been shown that arachidonic acid (a precursor of prostaglandins [PGs]) is mobilized from fetal membranes during human parturition being released from two specific glycerophospholipids during early labor. Interesting studies at the center note an increase in catecholamines concentration in amniotic fluid late in gestation suggesting that they may be regulators of arachidonic acid release. In vitro observations show that prostaglandin biosynthesis is stimulated by urine of human fetuses, increasing the conversion of arachdonic acid into prostaglandins. The stimulatory activity is greater with urine of term fetuses after onset of spontaneous labor. In contrast, throughout pregnancy human amniotic fluid contains an inhibitor of prostaglandin biosynthesis with the highest activity measured in early gestation. These investigations suggest that a signal for the initiation of labor may reside in a substance produced in or excreted by fetal kidneys into urine and amniotic fluid which would stimulate the biosynthesis of prostaglandins by the fetal membranes. PGs in turn, can cause contractions which are essential for labor and delivery.

RESEARCH ACCOMPLISHMENTS UNDER THE GRANTS PROGRAM

Selected scientific accomplishments during FY 1984 pertinent to the Section's five problem areas are highlighted in the following paragraphs:

High Risk Pregnancies: Pregnancy-induced hypertension continues to account for a major portion of perinatal morbidity and mortality. The etiology of the condition is unknown but both cardiovascular and renal physiology is disturbed in many patients and there are other abnormalities of blood flow and blood coagulation in this disorder. In addition, many patients exhibit a reduced blood volume. One investigator seeks to characterize renal function and blood volume regulation in both normal and abnormal pregnancies. Studies of one hormone, vasopressin (involved in blood volume regulation), have indicated that in normal pregnant women an expanded blood volume was recognized as normal by this regulatory hormone, which suggests that the vasopressin responses of pregnancy occur in response to plasma osmolality. The investigator believes that vasopressin could play a role in the oliguria and hypovolemia of preeclampsia.

Specific studies of the effects of angiotensin (a natural vasoconstrictive substance) are showing differential sensitivity of uterine and systemic vasculatures. The uterine vessels and particularly placental vessels appear to offer greater resistance to constrictor effects than systemic vessels. These findings suggest that the elevated angiotensin levels seen in normal pregnancies are responsible for the maintenance of systemic arterial pressure and uterine perfusion, but have little effect in increasing placental vascular resistance.

The transfer from the placenta to the fetus of nutrients such as amino acids, glucose and gases such as oxygen are dependent upon the quality of placental function. Placental transfer also seems to be dependent upon the rate of delivery of the substances to the placenta, that is, the rate of uterine blood flow. It had been a long term objective of one established investigator to develop the methodology to measure accurately the transfer of various substances in relationship to both uterine and umbilical blood flow to and from the sheep

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fetus in utero. In addition, this investigator has developed the techniques to measure such transfer in the very early fetus so that changes and development in placental transfer function can be studied over time.

Interesting genetic studies in rodents regarding the regulation of secretion of placental lactogen have shown paternal influences on hormone level and serum profile. Evidence suggests that mechanisms of secretory regulation vary at different points in gestation. Investigators are finding that arachidonic acid, a potent stimulator of placental lactogen release, probably acts by affecting cellular calcium concentrations.

Fetal Pathophysiology: Endocrine systems in the fetus of several species are active from mid-gestation onward. However, the exact role for these endocrine systems as regulators of metabolic fetal adaptations to stress and other functions is not clear. Some endocrine secretions are under nervous system control and several agents have been identified which transduce or translate neural signals to endocrine information. One investigator is studying the development of these transduced or translator systems in the neurohypophysis and pineal systems. Some of the hormones produced by them include vasopressin, oxytocin, and vasotocin. Such hormones are thought to participate in water and electrolyte balance in both mother and fetus. Indeed, an investigator found that vasopressin plays a role in reducing amniotic fluid volume during periods of hypoxia by decreasing fetal lung fluid production. In addition, a new oxytocin like hormone has been identified which could have a role in parturition.

One long term research project is examining the development of fetal thyroid function from the standpoint of neural control, regulation of thyroid hormone production, and the development of responsiveness to the hormone in various tissues. Such information is important to understand normal fetal growth and development, the impact of immature thyroid function in premature infants, and the mechanisms of disease in infants with thyroid abnormalities. Recent findings indicate that some of the metabolic effects of thyroid hormone are not produced in the fetus until late in gestation or even in the early newborn period. This may explain why infants with congenital hypothyroidism have few signs or symptoms of this disease at birth. Thyroid hormone has been shown to stimulate production of a variety of specific proteins involved in growth and maturation. For example, data supporting the view that thyroid hormone mediates its effects on epidermal maturation via epidermal growth factor in affected tissues is a recent finding of a CNPP-supported investigator.

Premature Labor and Birth: Relaxin is a polypeptide product of the human corpus luteum present in maternal serum throughout pregnancy. It is a structural homologue of insulin. It is suggested that insulin at high concentrations would occupy or affect relaxin receptors. One study is showing that human chorionic gonadotropin (hCG) can stimulate relaxin secretion in nonpregnant luteal phase women. These researchers have developed an in vitro system of long term human luteal cell maintenance. The aim of this study is to determine factors necessary for induction and maintenance of relaxin secretion from corpora lutea of nonpregnant women, and thus determine if relaxin plays a role in the establishment and maintenance of pregnancy.

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Relaxin is present in human decidua, in whole term placenta, with a higher concentration in the basal plate of the human placenta. One anatomist has been pursuing the hypothesis that, in guinea pigs, relaxin is produced and secreted by endometrial gland cells (EGC) and that the period of maximum effectiveness for the hormone is during late pregnancy just prior to parturition. Animals that can maintain pregnancy in the absence of a functional ovary with minimal or no hormone replacement therapy (human, pigs, rabbits, horses, etc.) produce relaxin in non-ovarian sources such as uterus or placenta. This researcher is examining the role of non-ovarian sources of relaxin in parturition, and the local or systemic effect they may have on such phenomena as softening of fetal membranes, pelvic ligaments and uterine cervix as well as placental detachment. Experiments utilizing primates are being accomplished to clarify the relationships among endocrine and vascular events during gestation and at parturition. Evidence is strong in a number of species that synthesis and release of prostaglandins (particularly PGF_2-alpha) initiate labor. Although investigations in women have failed to demonstrate a prepartum rise in circulatory prostaglandins, circumstantial evidence which supports the hypothesis that prostaglandins initiate human labor is persuasive.

Disorders of the Newborn: Over the last few years there have been significant advances clarifying the pathophysiology of Respiratory Distress Syndrome (RDS) which have resulted in the introduction of new methods to either prevent or treat this disease. Nevertheless it continues to be one of the most important causes of mortality and morbidity for the preterm infant. Functional lung immaturity in these infants results from inadequate amounts of surfactants (surface-active substances) to line the airspaces and prevent their collapse during expiratory movements. Investigative efforts in animal models are examining various factors responsible for the regulation of alveolar surfactant content in the immedate neonatal period. The role of fetal adrenal epinephrine was examined by decreasing production through maternal administration of a specific inhibitor of epinephrine synthesis. An association with decreased alveolar surfactant in the fetus was found indicating that endogenous epinephrine release has an important role in the regulation of surfactant production. Studies in premature lambs with RDS are showing that they have a small but significant ability to autoregulate their pulmonary blood flow, and that intravascular protein tends to leak more in aerated than in collapsed lung areas.

Another investigator is examining the toxic effect of oxygen upon developing lungs. Explants of lung tissue obtained from newborn rats show that functional cells can be isolated but that after 24 hours of exposure to oxygen there is a decrease in surfactant synthesis. Hyperoxic conditions for newborn rats during 72 hours result in an increase in anaerobic metabolism and a decrease in mitochondrial oxidative activities. These changes are adaptive and reverse to normal within two to three days after removal of the pups from the ambient of high concentration of oxygen.

The newborn infant is susceptible to many infections. A significant objective in neonatology is to develop improved methods for their early diagnosis, prevention, and treatment. Neonatal infections range from inapparent disease to sepsis which is rapidly progressive and carries a significant mortality rate. A comprehensive study of herpes simplex infection is showing that antibody titers of exposed infants are related to outcome. Indeed, not all exposed infants become ill, but

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among those infected, prematures are a disproportionate high group. The infection is not always maternal in origin; in a small number it was found that some asymptomatic mothers were married to men who had recurrent genital infections, and in other cases the origin was undetermined. Preliminary studies are showing that antiviral therapy of infected infants seems to influence their immune response.

Longitudinal studies in pregnant women and their offspring are being carried out in relation to cytomegalovirus infections (CMV). They are showing that the rate of acquisition in infancy and childhood is related to socioeconomic level favoring higher rates in low income populations and developing nations. Fifty percent of immune women who shed virus into breast milk and who breastfeed transmit CMV infection.

Studies are examining various phases of bilirubin production and excretion in infants. A noninvasive, simple measurement to rapidly identify infants with significant hemolytic disease has been perfected. It is based on the relationship between the concentration of carbon monoxide (CO) in a sample of breath, drawn through a nasopharyngeal catheter at end-expiration and the pulmonary excretion rate of CO. Using this technique preterm infants manifested an increased bilirubin production which was not prevented by early vitamin E supplementation.

With the introduction of new technology into the intensive care nurseries, infants with birth weights of <1500 grams are surviving. The assessment of the long-term outcome and growth patterns of the very low birth weight infants (VLBW) is an important objective. An interesting study is developing methods to determine the most favorable thermal environment for the VLBW in order to maintain a positive nitrogen balance and provide a way to improve their growth rates. To examine the best environment to reduce heat losses, an investigator is using a "Simulator of Neonatal Energy Transfer" (SONNET) instead of an infant, allowing for the estimation of the dry heat loss under given conditions.

The role of the cytochrome P-450-dependent system in the biotransformation of drugs is not completely understood. A group of investigators are examining various forms of cytochrome P-450 and determining those expressed during the perinatal period while examining the factors which may alter their expression.

The Sudden Infant Death Syndrome (SIDS) is defined as the sudden death of an infant or young child that is unexpected by history and where the death remains inexplicable after performance of an adequate postmortem examination remains the leading cause of death between the ages of one and twelve months.

Investigations during FY 1984 examined, among other areas, the relationship of sleep apnea and respiratory control to the occurrence of SIDS in young infants. Analysis of data obtained from children at risk for SIDS--i.e., siblings of SIDS victims, premature infants, babies of teenage mothers, and infants who frequently "stopped breathing"--showed disturbed electroencephalogram (EEG) activity and different sleep patterns than healthy infants.

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A CNPP supported epidemiologic study investigating the possibility of a familial genetic basis for the syndrome found a SIDS rate among subsequent live-born infants approximating 2 percent, equivalent to an odds-against-repetition of 50 to 1. Findings from this study also revealed that among twins if one dies of SIDS, there is only a 5 to 8 percent possibility that the other baby will succumb to SIDS, irrespective of zygosity. This low concordance rate in twins makes a genetic origin for SIDS very unlikely. These data provide strong support for developmental and environmental causative factors in SIDS.

STAFF ACTIVITIES

The staff of the Section represents the NICHD on groups and committees in both the public and private sector. Dr. Charlotte Catz is the NICHD representative to the DHHS Committee to Coordinate Environmental and Related Programs. She serves as an ex-officio member of the Maternal and Child Health Research Grants Review Committee of the Health Resource Services and Administration.
Dr. Donald McNellis is the NICHD liaison representative to the Committee on Fetus and Newborn of the American Academy of Pediatrics. He is also liaison to the Committee on Obstetrics: Maternal and Fetal Medicine of the American College of Obstetricians and Gynecologists. Dr. McNellis also serves as obstetric-gynecologic consultant to the Board for Correction of PHS Commissioned Corps Personnel Records.

Conferences and Workshops: The Section supported a workshop to discuss state-of-the-art and future research in fetal diagnosis and treatment. The workshop held in conjunction with the first annual meeting of the Fetal Medicine and Surgery Society took place in Washington, D.C. on June 9-11, 1984.

The Annual PERC Directors Meeting was held in March, 1984, with an emphasis on research issues concerning intrauterine growth retardation. Dr. Charlotte Catz chaired a symposium on SIDS at the XVII International Congress of Pediatrics, Manila, Philippines, November, 1983. She gave a presentation on SIDS research at the Annual Intra-Science Symposium on SIDS held in Santa Monica, California in February, 1984. She was an invited speaker at the annual meeting of the French Neonatal Society in Paris, France, May, 1984, and presented 2 papers entitled: Current Research in SIDS and Use of Ultrasounds during Pregnancy, Conclusions and Recommendations of an NICHD Consensus Development Conference.

Dr. Donald McNellis attended the meeting of the International Society for the Study of Hypertension in Pregnancy in Amsterdam, Holland, June, 1984.

Publications: The summary and recommendations of two CNPP workshops held in FY 1983 have been published.

Metcalfe, J., Catz, C., Clapp, J.F., Cureton, K.J., Fabro, S.E., Longo, L.D., and McNellis, D. "Summary Report on the NICHD Research Planning Workshop on Physical Activity in Pregnancy." Am. J. Perinatol. 1:2-4, 1984.

Read, M.S., Catz, C., Grave, G., McNellis, D., and Warshaw, J.B. "Introduction: Intrauterine Growth Retardation - Identification of Research Needs and Goals." Sem. Perinatol. VIII: 1:2-4, 1984.

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Nutrition and Endocrinology Section

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PROGRAM ACTIVITIES

EMPHASIS AREAS

The Nutrition and Endocrinology Section supports research and training on developmental aspects of nutrition, endocrinology, and physical growth.

FINANCIAL SUPPORT

As of June, 1984, the Section supported 197 projects at a level of $21,340,000. These projects are analyzed according to programmatic mechanism in Table 2c. Two-thirds of the total budget supported nutrition-related research and one-third supported research on developmental endocrinology and physical growth. In FY 1984 the Section received 253 research grant and research training grant applications. Of these 144 were approved and 45 were funded by July 1, 1984.

RESEARCH TRAINING

The Section currently funds four Institutional (T-32) National Research Service Awards (NRSAs). Two of these are devoted to developmental aspects of nutrition. The post-doctoral fellows supported by these awards are pursuing nutritional needs of prematurely-born babies and babies born at term, especially amino acid and essential fatty acid requirements. The other two Institutional NRSAs are concerned with developmental aspects of endocrinology and physiology. The post-doctoral fellows supported by these awards are working on projects that vary from studies of mechanisms of gonadotropin release to opiate receptor function. The Section also funds six Individual (F-32) NRSAs in developmental endocrinology and two in nutrition.

CONTRACT PROGRAM

The Section on Nutrition and Endocrinology has been especially concerned with the composition, health values, and developmental importance of human breast milk for the normal newborn as well as for the high-risk infant. To meet the special needs of this field, a coordinated research contract program was established to expand knowledge on the detailed composition and function of the many constituents of human milk. As a result, this unique biological fluid is now recognized as a valuable source of nutrients, growth factors, and antimicrobial agents for newborn infants, particularly those with low birth weight. In FY 1984, the 11 contracts in this area amounted to $1,731,000.

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Table 2c.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
NUTRITION AND ENDOCRINOLOGY SECTION

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	197	21,340	172	18,624	148	16,399	15	1,876	9	348	12	567	13	2,149
Developmental Gastroenterology	22	1,929	22	1,929	22	1,929	-	-	-	-	-	-	-	-
Childhood & Developmental Nutrition	18	1,646	15	1,381	15	1,381	-	-	-	-	3	264	-	-
Infant Nutrition	50	6,006	38	4,258	22	2,347	15	1,876	1	34	1	17	11	1,731
Obesity & Antecedents of Adult Disease	11	1,712	11	1,712	11	1,712	-	-	-	-	-	-	-	-
Behavioral & Cultural Aspects of Nutrition	13	1,630	12	1,314	11	1,275	-	-	1	[illegible]9	-	-	1	316
Maternal-Fetal Nutrition	10	1,020	10	1,020	9	978	-	-	1	42	-	-	-	-
Adolescent Nutrition	1	30	1	30	-	-	-	-	1	30	-	-	-	-
Nutritional Status	2	47	2	47	1	5	-	-	1	42	-	-	-	-
Developmental Endocrinology	62	6,224	54	5,938	50	5,778	-	-	4	161	8	286	-	-
Developmental Physiology	4	460	4	460	4	460	-	-	-	-	-	-	-	-
Physical Growth	4	636	3	534	3	534	-	-	-	-	-	-	1	103

Notes: 1) Excludes the scientific evaluation grants.
2) Subprojects of program projects are counted individually.

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RESEARCH HIGHLIGHTS

MATERNAL-FETAL NUTRITION

One of the most important of the Section's programs, especially from a preventive point of view, is that of maternal-fetal nutrition. Using an animal model system, an investigator has shown that zinc deficiency in the pregnant rat causes a 38 percent incidence rate of microphthalmia (malformations of the eye) in developing fetuses. The pathologies range from no visible eye to only slight reduction in size. These studies represent the most significant effort to date to understand the teratogenic effect of zinc deficiency.

A major unsolved problem in the area of maternal-fetal nutrition is that of intrauterine growth retardation (IUGR). A sheep model of IUGR has been developed to assess the feasibility of intrauterine nutritional therapy delivered directly to the fetal stomach. Results show that infusion of a solution of glucose and amino acids during the period of maternal dietary restriction significantly increases birth weight and crown-rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. It also has been shown that during maternal zinc deficiency the fetus maintains a higher concentration of zinc than is in maternal blood.

INFANT NUTRITION

Research interests here include the nutrient requirements of normal, premature, and growth-retarded infants, as well as analysis of human milk, cow's milk, and synthetic formulas in relation to optimal infant development.

For 10 years NICHD has supported a major program project which has developed much of the benchmark normative data on physical growth and nutritional needs during early infancy. This group is now using stable isotopes and a new electromagnetic device that has the potential of providing useful data on the fat-free body mass of normal infants. In addition, they are assessing food consumption, energy expenditure, growth and nutrient interactions in the management of low birth weight infants. They have found that in some soy-based formulas designed for premature infant feeding, the actual calcium ingestion is quite variable due to precipitation of calcium from some formulas which then remains in the feeding bottle.

A major difficulty in the clinical management of the sick infant or child is knowing whether they are capable of digesting specific food components. Tests of digestive function usually are very expensive, time consuming and subject the patient to a degree of risk or discomfort. One investigator has shown that the measurement of hydrogen and methane in the infant's breath after a test dose of specific dietary protein may be used as a non-invasive technique for the measurement of digestive function. It has proven to be quick, reliable, and relatively inexpensive.

Another investigator is studying carbohydrate metabolism in premature and newborn infants with compromised intestinal function. Glucose polymers provide a calorically dense, low osmolar source of carbohydrate used in a number of infant formulas. These studies are exploring the optimum form of polymer that

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could be used as a carbohydrate source in the treatment of infants with gastrointestinal dysfunctions such as intractable diarrhea, the short bowel syndrome, and post-viral gastroenteritis. These studies will provide a better understanding of carbohydrate intolerance in infants with gastrointestinal dysfunction and a rational basis for managing them.

The biochemical immaturity of premature infants presents challenging problems that must be solved in order to design appropriate feedings for their enteral and parenteral nutrition. For example, recently much has been learned about the complicated composition of human milk and how it reflects the metabolic needs of the newborn. Milk is not just a fluid containing nutrients. It is composed of a large array of constituents, many of which have important non-nutritive functions. The structure of the milk fat globule exemplifies the complicated packaging of milk components. The globule is surrounded by a membrane that is derived from the breast milk cell. It has recently been shown by ultramicroscopic observation that this membrane has whisker-like filaments on its outer surface. Human milk is the only species examined so far that has these structures. This observation may be the first clue as to how specific lipases are able to recognize milk lipids for the purpose of digestion. Additionally, it has been demonstrated that the fats present in the milk fat globule are not available for lipolytic digestion until the globules come in contact with bile salts in the small intestine. Thus, milk appears to contain a mechanism to limit the digestion of its components until they reach the proper site for digestion.

DEVELOPMENTAL GASTROENTEROLOGY

The goal of the Section's program in developmental gastroenterology is to understand events governing development of the gastrointestinal tract from fetal life to adulthood. Emphasis is placed on the role of nutrients as effectors of gastrointestinal development.

Neonatal events impose unique adaptive needs on the gastrointestinal tract. It has been shown that the newborn infant possesses only a limited supply of energy reserves which are stored as body fat, and that the infant has only a moderately developed intestinal tract. At birth, nature orchestrates the release of a complex series of secretions from the oral cavity, stomach, and intestine, each of which plays a critical role in digestion and absorption. Several studies are underway on the progression of the digestive processes that appear near the time of birth. It is clear that absorption of fats from the diet are critical to the newborn infant's energy needs. Therefore, an animal model system has been developed that allows for analysis of bile acid secretion in the newborn, and another study is focused on the role of fat-digesting enzymes secreted in the mouth and in the stomach.

BEHAVIORAL ASPECTS OF NUTRITION

The Section supports research that emphasizes the roles played by various nutrients in cerebral and somatic development. These studies are designed to ascertain the effects of general and specific kinds of undernutrition on physical growth and cognitive development during infancy and childhood. For example, iron deficiency as well as iron-deficiency anemia have been linked to various cognitive deficiencies during development. An NICHD investigator has

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shown that anemic infants exhibited fearful, tense and withdrawn behavior during evaluation but showed no differences during play. However, the mothers of anemic infants behaved differently from those of the non-anemic group. Paradoxically, the mother frequently initiated interaction with their anemic infants. This pattern of maternal behavior may provide an explanation for the normality of the anemic infants' behavior in play despite their disturbance during developmental assessments.

DETERMINANTS OF OBESITY

A crucial research issue that is being addressed by the Section concerns the antecedents of obesity. The ultimate goal is to identify determinants of obesity in childhood and adolescence in order to identify those individuals at high risk of becoming obese later in life and to design various kinds of preventive therapy.

The Section continues to support a 15-year longitudinal study of the development of obesity in 170 children followed from birth. The research focuses on the association of childhood obesity with present and past environmental factors, including diet, physical activity, early parental views and wishes about their child's body conformation, and patterns of diet and physical activity. Obesity at 12 years assessed by triceps skinfold and sum of 4 skinfolds was negatively correlated with past physical activity level. No correlation was observed between caloric intake and skinfolds. Early parental attitudes and wishes regarding their children, and certain characteristics of their children and child rearing behaviors of parents have shown no relationship to obesity in the children, including breast versus formula feeding, early feeding of solid foods, and the child having a "sweet tooth." Early prediction of adolescent obesity seems to be impossible before the age of 2 years. Another jump in predictability occurred at 6 years. The correlation coefficient between 14-year and 6-year skinfolds was .60. Separate examination of the boys and girls illustrated that early skinfold measurements were more predictive of later obesity in girls than in boys.

NICHD-supported investigators have developed behavioral paradigms to control body weight in high-risk children. The study involves long-term follow-up of a group of preadolescent obese children who participated in a trial to determine the effects of targeting parent and child or child alone in a behavioral weight control program. After three years of follow-up, these investigators showed different treatment effects: 83 percent of the children who significantly lost weight at eight months were still not obese if their parents participated, while only 30 percent of children in the child alone group maintained the weight loss.

DEVELOPMENTAL ENDOCRINOLOGY AND PHYSICAL GROWTH

The field of developmental endocrinology encompasses studies of hormonal influence on growth and development, studies of growth factors, and studies of the development of the hypothalamic-pituitary axis in relation to the thyroid, adrenal glands, and gonads.

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GROWTH HORMONE (GH) AND GROWTH HORMONE RELEASING FACTOR (GRF)

Recently several exciting discoveries have been made in the therapy of short children which coincide with the advent of biosynthetic hGH. One investigator has identified a group of short children who are not demonstrably deficient in hGH but who have low levels of somatomedin C and who respond to the administration of exogenous hGH with accelerated linear growth. Others have shown that some short children with apparently normal hGH and normal somatomedin C will respond to the administration of exogenous hGH with accelerated linear growth. The ability of exogenous hGH to promote linear growth in the absence of demonstrable hGH deficiency, coupled with the expected availability of large amounts of biosynthetic hGH, will prove beneficial in the clinical management of short children in the near future.

The recent isolation and purification of hypothalamic human GRF presents a major clinical research opportunity in the area of short stature. For the first time conditions of hypothalamic growth failure can be distinguished from conditions of hypopituitary growth failure. When GRF becomes more widely available for experimentation, diagnostic tests of the etiology of short stature can be devised, and clinical trials of the efficacy of GRF in short stature can be initiated. At a more basic level, GRF can be used to study mechanisms of hormone action. The actions of GRF on pituitary somatotropes can now be studied in regard to transcription of the growth hormone gene, translation of growth hormone messenger RNA, post-transitional alterations of the prohormone, and release of growth hormone into the circulation.

Recently two investigators reported on the growth hormone response to synthetic GRF in non-GH deficient subjects and GH deficient patients. The mean peak GH response of non-deficient children after treatment of GRF was similar to that of non-deficient young men. Of 20 patients with severe GH deficiency 17 responded to GRF, but the mean peak plasma GH concentration was less than that of the non-deficient group. Patients with isolated GH deficiency had responses similar to those with multiple pituitary hormone deficiencies. GH responses of the growth hormone deficient children correlated negatively with chronologic age. GRF induced higher plasma GH levels in the growth hormone deficient patients than did arginine, insulin, or L-dopa. Thus, the GRF test is clearly useful for assessing GH reserve.

The GH response to synthetic GRF in the growth hormone deficient children is consistent with a hypothalamic abnormality as the cause of their GH deficiency and supports the potential therapeutic usefulness of GRF or an analog of GRF in these patients.

EPIDERMAL GROWTH FACTOR (EGF)

Landmark discoveries also have been made in the growth factor field, including purification and sequencing of epidermal growth factor. It has recently been shown that the EGF-receptor complex is closely associated with a tyrosine-specific protein kinase. This discovery has implications for understanding certain aspects of the hormonal control of growth as well as the cause of uncontrolled cell proliferation in tumors, because transformation of cells by several RNA tumor viruses seems to be mediated by virally-coded protein kinases which also phosphorylate tyrosine.

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One investigator has shown that binding of EGF to the receptor is followed by rapid activation of the tyrosine-specific protein kinase and internalization of the EGF-receptor complex. The hypothesis is that internalization of the receptor facilitates the interaction of the kinase portion of the receptor with nuclear membrane components. The mechanism by which EGF stimulates growth remains controversial. The suggestion that endocytosis may facilitate kinase action is a novel idea which may well provide an insight into this enigmatic issue.

TREATMENT OF PRECOCIOUS PUBERTY WITH LHRH ANALOGUE

Recently a promising treatment has been developed for the perplexing condition known as idiopathic central precocious puberty in which young children, or even toddlers, acquire mature sexual organs and secondary sexual traits. Within the past three years many cases of female precocious puberty have been treated successfully with a synthetic agonist of luteinizing hormone releasing hormone ($LHRH_a$). Initial results are most encouraging in that patients' gonadotropin levels revert to undetectable levels, and their sexual characteristics regress to pre-pubertal status. This year NICHD-supported investigators reported on the results of $LHRH_a$ therapy in males. They noted that the analogue is capable of reversing the clinical features of sexual precocity, abolishing the pulsatile release of gonadotropins and testosterone production, retarding skeletal maturation, and slowing growth velocity from a mean of 13.5 cm/yr. to 5.5 cm/yr. No deleterious side effects have been observed.

CONGENITAL ADRENAL HYPERPLASIA

New data have shown novel clinical, genetic, and biochemical aspects of both the simple virilizing and the salt-wasting forms of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH). By examining cases of genetic recombination in 150 Caucasian families between the HLA-B locus and the gene or genes for 21-hydroxylase, NICHD investigators established that the alleles Bw47, B5 and B14 are most commonly associated with the simple virilizing form of classical 21-hydroxylase deficiency (Relative Risks=2.5; 2.5; 7; respectively) and that the alleles B40 and Bw47 are those most commonly associated with the salt-wasting form of CAH (Relative Risks=3; 15; respectively). These data strongly suggest that the simple virilizing form and the salt-wasting form of 21-hydroxylase deficient CAH are caused by different mutations at the 21-hydroxylase locus (or loci). Late onset and cryptic forms of the disorder are associated with genetic markers HLA-B14, HLA-DR1, and Properdin factor BfS. Individuals with the cryptic form of CAH appear to be double heterozygotes and carry one allele for classical CAH and one for cryptic CAH.

DEVELOPMENTAL NEUROENDOCRINOLOGY

The developmental neuroendocrinology program emphasizes studies of the effects of hormones on the developing nervous system. It has recently been discovered that two discrete nuclei of motor neurons located in the mammalian spinal cord control the muscles of ejaculation. These spinal cord nuclei are virtually absent in females, as are the muscles they innervate. NICHD-supported investigators proved that androgens act during a critical perinatal period to determine the number and size of these motor neurons. They also showed that just a single injection of testosterone given to a female rat pup at this critical time will produce a

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masculinized spinal cord containing nuclei of motor neurons which innervate ejaculatory muscles normally absent in the female. Conversely, antiandrogens given to male pups perinatally results in a spinal cord indistinguishable from that of female rats. The mechanisms responsible for these observations are now being studied.

HORMONES AND THE CAUDATE NUCLEUS

A sophisticated technique has been developed tc measure the neurochemical and behavioral effects of local hormone infusions into the caudate nucleus of the brain of conscious rats. Recently one investigator infused prolactin in nanogram amounts deep into the caudate nucleus. Within minutes he observed pronounced elevation of dihydroxyphenylacetic acid (a metabolite of dopamine) coupled with intense grooming and yawning behavior. This effect appears to be sex-specific, operating only in male rats, and appearing only after puberty. These studies are key because little is currently known of the actions of hormones on the caudate nucleus which connects the neuroendocrine hypothalamus with motor, sensory and cognitive functions of the cerebral cortex.

FORWARD PLANNING

NICHD FIVE YEAR PLAN ON DEVELOPMENTAL ENDOCRINOLOGY AND PHYSICAL GROWTH

In FY84 the Section on Nutrition and Endocrinology embarked on a detailed evaluation of its current research program in developmental endocrinology and physical growth in order to develop a Five Year Plan for these areas of research. Seven workgroups were formed, each headed by a distinguished chairman. Dr. Selna Kaplan is serving as overall chairperson. With her assistance, the recommendations of these workgroups will be incorporated into the final research plan by the end of FY 1985.

SURGEON GENERAL'S WORKSHOP ON BREASTFEEDING AND HUMAN LACTATION

Staff of the Section participated in the planning for the Surgeon General's workshop entitled "Breastfeeding and Human Lactation" which was held at the University of Rochester on June 11-12, 1984. The workshop drew experts from across the country and from a dozen disciplines to formulate national recommendations in this important area. Eight workgroups were established to explore decision-making, support services, work and sociocultural determinants, and promotion of breastfeeding. Each group made specific recommendations that are being incorporated into a report to be published in the fall of 1984. The research recommendations will guide in part future CNNE program development.

NICHD DIRECTOR'S CONFERENCE ON THE USES AND POSSIBLE ABUSES OF BIOSYNTHETIC HUMAN GROWTH HORMONE

Staff worked closely with Dr. Lipsett and a planning group of pediatric endocrinologists to organize this conference, which was held in Baltimore on November 22-23, 1983. The conference provided an opportunity to discuss the ethical and social issues involved in the use of biosynthetic human growth hormone. The conferees concluded that any use of biosynthetic human growth

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hormone except for medically diagnosed children of short stature had to be considered experimental. They agreed that using the synthetic growth hormone to stimulate additional growth in normal children for cosmetic or athletic reasons would be unethical. Research recommendations also were formulated. Proceedings of this conference will be published shortly in the New England Journal of Medicine.

STAFF LIAISON ACTIVITIES

The professional staff of the Section represents the NICHD on a number of groups and committees in both the public and private sectors. Dr. Gilman Grave, the Section Chief, represents the Institute on the NIH Diabetes Mellitus Coordinating Committee as well as on the Diabetes Mellitus Interagency Coordinating Committee. He serves as the alternate NICHD member of the National Diabetes Advisory Board. Dr. Grave also represents the NICHD on the trans-NIH Workgroup on Inherited Metabolic Disorders.

Dr. Thorsten Fjellstedt represents the NICHD on the NIH Digestive Diseases Coordinating Committee and also is liaison to the U.S.-Japan Cooperative Biomedical Sciences Panel on Malnutrition. He serves as the alternate NICHD member of the National Digestive Diseases Advisory Board. Dr. Fjellstedt serves as NICHD liaison representative to the Committee on Nutrition of the Mother and Preschool Child of the Food and Nutrition Board of the National Academy of Sciences. He also serves as liaison representative to the Committee on Nutrition of the American Academy of Pediatrics. Dr. Fjellstedt acts as the NICHD designated representative to the Board of Scientific Counselors of the USDA-Children's Nutrition Research Center in Houston, Texas.

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Mental Retardation and Developmental Disabilities Branch (MRDD)

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OVERVIEW

Few problems related to human development are more complex and challenging than mental retardation, a lifetime condition requiring study of the full range of developmental variables. Mental retardation weighs heavily on the individual, his family, the community and the economy and resources of the nation. The complex phenomena included under the term mental retardation, or MR, are the product of multiple interacting biological, behavioral, and social variables.

Mental retardation research at the NICHD is supported mainly through the Institute's Mental Retardation and Developmental Disabilities Branch (MRDD), in the Center for Research for Mothers and Children (CRMC). Other branches within the extramural and intramural programs of the NICHD have made significant contributions in the area with investigations into the damaging effects of complicated pregnancies, difficulties during birth, and adverse factors in early infancy, as well as the effects of nutritional deficiences and imbalances. Other more indirect contributions have been made through research aimed at improving the health of mothers.

In its programming, the MRDD Branch emphasizes research aimed at preventing MR, with special attention to elucidating the cause of Down syndrome, the most common genetically determined condition associated with mental retardation. Also given high priority are studies of "high-risk" infants, babies born under conditions associated with susceptibility to later developmental retardation. Family variables and parent (caregiver) interactions strongly influence the development of high-risk infants. Other influences include preschool and school and the larger community. These factors often determine whether, as the child matures, he or she either drops from risk status or requires continued support to minimize residual deficits. Research that seeks to understand these processes and to find means to increase their positive effects on development is emphasized.

PROGRAM ACTIVITIES

FINANCIAL SUPPORT

The MRDD Branch supports research and research training related to the biological, behavioral and social processes that contribute to or influence the development of retarding disorders. To accomplish its mission, the branch uses research grant mechanisms, supports special research facilities called Mental Retardation Research Centers (MRRC's), provides contract support for development of new research resources, and disseminates information to the scientific community and the public.

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More than 200 mental retardation syndromes have been identified, and new ones are discovered each year. Each requires fundamental research into the underlying processes, as well as studies designed to meet the unique needs of the afflicted children. Therefore, the branch supports a comprehensive program of MR research concerning the etiology and pathophysiology, epidemiology, diagnosis and evaluation, prevention and amelioration of mental retardation (Table 3).

RESEARCh TRAINING

Institutional training grant awards providing both pre- and postdoctoral stipends are the mainstary of the branch's training award program. In FY 1984, the branch supported 14 institutional training grants which provided training for 65 biomedical trainees and 58 trainees in the behavioral and social sciences for a total of 123 trainees. This represents a significant drop since the 1981 Report to Council at which time a total of 160 trainees were supported.

Career and fellowship awards are made and complement the institutional training grant award program. In FY 1984 the branch supported 8 career awards and 1 fellowship, a slight increase over the level supported in FY 1981.

MENTAL RETARDATION RESEARCH CENTERS (MRRCs)

More than half of the MR research supported by the MRDD Branch is conducted in the MRRC's. The primary objective of the Mental Retardation Research Centers program is to provide facilities for a cohesive, interdisciplinary program of research and research training in MR and related aspects of human development. Currently there are 12 centers distributed throughout the nation. Their construction was authorized by Public Law 88-164, Title I, Part A. Under the provisions of the Act, the 12 Centers agreed to use the constructed facilities for their intended purpose for a minimum of 20 years. On average, the Centers have now completed 14 years of this obligation.

The NICHD has provided the centers with core grants (a program project grant mechanism) to facilitate program coordination and to support central facilities. In FY 1984, these centers received about $7.0 million in core grants. Total support for MRRC operations -- provided by the NICHD and other NIH institutes, other Federal agencies, foundations and other sources -- was approximately $30 million. About 15 percent of the total support to the MRRC's came from local sources. In addition to the constructed centers, the NICHD supports a specialized research center focused on research on Down syndrome.

Ten of the 12 centers are administratively and functionally joined with a University Affiliated Facility (UAF), supported, in turn, through the Bureau of Community Health Services and the Administration on Developmental Disabilities. The UAF's were authorized by Public Law 88-164, Title I, Part B, to provide clinical training for the professions involved in treating mentally retarded individuals. They also provide a means for translating into services the new methods of treatment and care developed through research.

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Table 3.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES BRANCH

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	471	31,563	440	28,800	99	10,778	331	17,549	10	473	89	1,607	12	1,156
Etiology/Pathophysiology	245	17,082	233	15,978	50	5,506	178	10,229	5	244	10	899	2	205
Epidemiology	9	719	4	422	2	371	2	51	-	-	-	-	5	296
Diagnosis and/or Evaluation	162	10,231	151	9,103	35	3,833	114	5,194	2	76	9	708	2	420
Prevention	13	1,017	10	781	2	380	8	402	-	-	-	-	3	236
Amelioration-Education	29	1,849	29	1,849	6	425	23	1,424	-	-	-	-	-	-
Amelioration-Medical Treatment	9	576	9	576	3	259	3	165	3	153	-	-	-	-
Other (includes implementation grants)	4	89	4	89	1	5	3	84	-	-	-	-	-	-

Notes: 1) Excludes the scientific evaluation grant.
2) The Minority Biomedical Support grants (S06) are included in the research projects.
3) Subprojects of program projects are counted individually.

NICHD-OPE-PAS
July 18, 1984

The range of research studies being conducted in the MRRC's encompasses every known major dimension of the problem. This concentration of activity is supplemented by the work of investigators located in other universities, agencies, and research settings. The activities described in the section which follows represent a few of the research accomplishments and highlights from the Branch portfolio during this fiscal year.

RESEARCH HIGHLIGHTS

BIOMEDICAL RESEARCH

Genetics and Genetic Disorders

Advances in medicine and surgery, and application of public health measures such as improved nutrition and immunization programs, have resulted in a diminished contribution of environmental factors and infectious diseases to mortality and morbidity. As a consequence, genetic disorders have become increasingly prominent in the etiology of human diseases. Surveys of pediatric hospital admissions have shown that 10-25 percent of patients have a disorder which is at least partly genetic in causation, and 5 percent have a disorder which is entirely genetic in origin. Similar surveys of adult in-patients have revealed a prevalence of only about 1percent with a unifactorial or chromosomal disorder. This low prevalance could be attributed to the fact that such disorders lead to early death, or if they are compatible with survival into adulthood, they usually do not warrant hospital admission. Furthermore, when the surveys were done, the genetic heterogeneity in such disorders as diabetes mellitus, coronary heart disease, peptic ulcer and hypertension was not realized.

Surveys of live-born infants have shown that 3-4 percent have genetic abnormalities. About 6 per 1,000 unselected newborns have major chromosomal abnormalities such as Down syndrome; 7 per 1,000 have autosomal dominant genetic disorders such as Huntington's disease; 2.5 per 1,000 have autosomal recessive disorders such as phenylketonuria; 0.5 per 1,000 have X-linked unifactorial disorder such as Duchenne muscular dystrophy; and about 20 per 1,000 have multifactorial disorders caused by an interaction of multiple genes and exogenous or environmental factors exemplified by spina bifida.

Cytogenetics

The contribution of chromosomal abnormalities to reproductive outcome can be gleaned from the following table:

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INCIDENCE OF CHROMOSOMAL ABNORMALITIES BY POPULATION GROUPS

First trimester spontaneous abortion	50-60%
Children evaluated because of suspected cytogenetic abnormalities	32.2%
Infants dying in the perinatal period	5.8%
Full-term low birth weight infants	2.2%
Non-selected newborn infants	.6%

The NICHD amniocentesis registry showed that 30 fetuses of 950 women (3.1 percent) who had amniocentesis for cytogenetic indications were found to be abnormal.

Down Syndrome: Down syndrome is the most common and readily identifiable genetic condition found among the mentally retarded. Its incidence has been decreasing for the past several years. In 1960, the incidence of Down syndrome was 1.33 cases per 1,000 births, while in 1980 the incidence was 0.73 per 1,000 births, a 45percent drop in frequency. Demographic shifts in the U.S. population were the primary reasons for the decrease in incidence of Down syndrome.

It is a well known fact that the incidence of Down syndrome increases with advancing maternal age, particularly at age 35 and over. The number of babies born by women in this age group dropped from 10.8 percent in 1955 and 1960 to 4.6 percent in 1980, a decrease of about 51percent. But this trend will probably change in the future. Babies born during the "baby boom" of the 1950's are getting older. Census Bureau projections show that female population in the 35-44 year group peaked in 1960 to 34 percent. The number of women in this age group has been going up since 1970 when the proportion dropped to an all time low of 24.7 percent. In 1983, 27 percent of women were 35-44 years and it is projected to increase to 33 percent in 1990. It can be anticipated that, based on these population projections, the incidence of Down syndrome will go up, with a concomitant increase in the requests for amniocentesis or first trimester prenatal diagnosis using chorionic villus sampling.

Because proportionately more infants with Down syndrome have been born to women over 35, it has been postulated that the mother was the more likely source of the extra chromosome. Females are born with all the ova that they will ever have and are, therefore, vulnerable to endogenous and exogenous influences, while the male produces sperm continually. It is not surprising, therefore, that most of the research on Down syndrome have concentrated on the maternal contribution to trisomy 21. With the advent of new staining techniques, it is now possible to determine, in about 80 percent of cases, the parental source of the extra chromosome 21. Several studies have demonstrated

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that, in about 20 to 25 percent of Down syndrome, the father is the source of the extra chromosome. A number of population surveys have failed to demonstrate a paternal age effect on the incidence of Down syndrome as it does with maternal age.

The Institute is supporting a number of studies dealing with various aspects of Down syndrome, including basic studies relevant to the molecular biology of the condition. Six genes have now been "mapped" on human chromosome 21. Since the basic molecular structure and function of these genes are difficult to study on human subjects, a mouse model has been developed which, when trisomic for chromosome 16, shows genetic homology to Down syndrome. Mice with trisomy 16 are smaller than their normal litter- mates, have a high frequency of congenital heart defects, small and less cellular brain, and a relatively flat skull base. These abnormalities are commonly found in Down syndrome. In addition, three of the six genes that have been "mapped" on human chromosome 21 have also been "mapped" on mouse chromosome 16. Of the genes assigned to human chromosome 21, three (SOD-1, PRGS, PFKL) have been regionally assigned to band 21q22, the "Down syndrome" region of the chromosome. Mice trisomic for the distal 1/8 of mouse chromosome 16 will be selectively bred as a more specific genetic model of human trisomy 21.

One of the MRRCs supported by NICHD devotes its research efforts exclusively to Down syndrome. The MRRC at the University of California in San Francisco was established in September, 1982. It differs from the other MRRCs in that it is a specialized research center with both direct research and core support but without the provisions for the construction of new facilities. The research thrust of the center represents the convergence of three elements that have been of long standing interest to the investigators. The first deals with the biology of interferon in trisomy 21 cells and with the effects of interferon on the trisomic immune system. The second element deals with the general problem of aneuploidy, particularly in the mechanisms by which chromosome imbalance results in harmful effects on development and function. The third element deals with the development of a mouse model for human trisomy 21. The mouse model is primarily used for gene mapping studies using somatic cell genetic techniques.

Fragile X Syndrome: A male excess of approximately 50 percent among institutionalized and community-based subjects was demonstrated by previous surveys on the prevalence of mental retardation. In the past, social and behavioral variables were the reasons given for a higher prevalence of mental retardation in males. More recently, however, increasing number of studies are being pursued to ascertain the biological reasons to explain this phenomenon. It is now estimated that 25 percent of X-linked mutations lead to, or are associated with, mental retardation.

The Fragile X syndrome is a subgroup of X-linked genetic abnormalities which is becoming increasingly recognized as one of the most significant causes of mental retardation. Although precise information on its prevalence is not yet available, it has been estimated to be 1 in 2,000. This estimate, however, was based on a number of surveys done mainly on mentally retarded subjects. The condition is one of the most common diagnosable forms of mental retardation, and is second only to Down syndrome in frequency among children with a chromosomal abnormality.

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The clinical manifestations of the syndrome include enlarged testes; mental retardation; low-set ears that are posteriorly rotated and greater than normal in length, and soft due to an apparent cartilage hypoplasia; normal to slightly enlarged head circumference; a high and prominent forehead; prominent supraorbital ridges; a long and narrow face with slight mid-face hypoplasia; prominent mandible; and connective tissue dysplasia. The most consistent features are enlarged testes, which could be three to four times normal volume, and mental retardation. About one-third of carrier females are either mildly to moderately mentally retarded or have non-specific learning difficulties. In addition, there is an inverse correlation between intelligence in the carriers and the frequency of the marker X chromosome.

In 1981, an NICHD-supported investigator succeeded in demonstrating the marker X from cultured fibroblasts obtained from two affected males and a carrier female. By culturing fibroblasts in a medium without thymidine but with normal concentration of folic acid, and adding 5-fluorodeoxyuridine (FUdR), he was able to induce marker X expression. This led the way to the successful demonstration of the marker X from cultured cells obtained following amniocentesis from carriers of the Fragile X syndrome.

In April, 1983 the NICHD sponsored an International Workshop on the Fragile X syndrome. Despite significant advances in our knowledge of the syndrome, there are a number of issues that are yet to be resolved. The panel's recommendations included the following:

1. The spectrum of clinical manifestations and neuropsychological dysfunction in Fragile X subjects and obligate carriers should be defined. Objective measures should be used instead of relying on subjective impressions.
2. More studies on tissue culture techniques are needed.
3. DNA probe repository and cell banks for future research on the X chromosome should be established. Studies applying recombinant DNA techniques should be encouraged.
4. Studies dealing with early diagnosis of the syndrome and carriers should be initiated.
5. More research aimed at prenatal diagnosis of the condition is needed.
6. The role of folic acid in causing or correcting the syndrome should be determined.

These recommendations were endorsed by the Genetics and Cytogenetics Committee which was convened by the MRDD Branch to help staff develop its forward plan.

A follow-up meeting on X-linked mental retardation, with a special emphasis on the Fragile X syndrome, is being organized in conjunction with the annual meeting of the Human Genetic Society of Australia. It is appropriate that the Australian host the next workshop as it is research done in their country that has been largely responsible for the resurgence of interest on the Fragile X syndrome.

Gene Mapping: Genes, the basic units of heredity, are located linearly on the chromosomes. By using somatic cell genetic techniques and linkage studies in families, one can determine the exact location of a gene on a chromosome. As previously noted, NICHD-supported investigators are engaged in research to

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"map" the genes particularly on chromosome 21 and the X chromosome. In August, 1983, the Institute provided partial support to the Seventh International Workshop on Human Gene Mapping, which was held at the University of California, Los Angeles. The workshop focused on the establishment of gene assignments on chromosomes and the promotion of information exchange among scientists with different backgrounds but with interests in gene "mapping." Knowledge of the human gene "map" has basic and clinical implications. At the basic science level, gene map information increases knowledge of genetic recombination and has implications for evolution; gives insight into how expression of genes is affected by location (position effect); improve understanding of chromosome structure; help to identify genetic control mechanisms; and give insight into the pathogenesis of malignancy associated with chromosome changes. At the clinical level, gene mapping information has implications for diagnosis and genetic counseling; identify persons at risk before a disease manifests clinically both prenatally and postnatally; identify from which parent a chromosome abnormality has arisen, which can then help to focus the studies on the causes of chromosome change in the responsible parent; and to help understand the pathogenesis of the abnormal phenotype associated with the chromosome anomaly.

Dr. Woo's successful cloning of the phenylalanine hydroxylase gene (see subsequent discussion under Inborn Errors of Metabolism) is a prime example of the productive application of recombinant DNA technology in understanding the molecular biology of mental retardation.

Arginase is an enzyme required for urea cycle metabolism and its deficiency results in hyperargininemia. The condition is characterized by progressive mental and neurological deterioration. Investigators from the Mental Retardation Research Center at UCLA have succeeded in cloning the cDNA for rat liver arginase. They have also demonstrated the suitability of the rat arginase cDNA to probe for human liver arginase clones. The breakthrough that the investigators have achieved by cloning the rat liver arginase will be used to study its implications for intermediary metabolism in arginase deficiency and its treatment.

Congenital Hypothyroidism: Newborn screening programs have shown that approximately one in 4,500 newborns has primary hypothyroidism. Less than 5 percent of those found to have the disorder were suspected of having hypothyroidism before screening.

Congenital hypothyroidism results in intellectual impairment and neurologic dysfunction unless diagnosed and treated early in infancy. An NICHD-sponsored project is seeking to determine whether early diagnosis and treatment of congenital hypothyroidism would result in the prevention of permanent damage to the central nervous system. The results of the study show that the global I.Q. score of the hypothyroid children tested through the age of five years have the same distribution as those of their controls. The number of hypothyroid children identified by newborn screening, their ages, and their developmental profile are shown on the following page.

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	PATIENTS			CONTROLS		
	No.	Mean	S.D.	No.	Mean	S.D.
Bayley MDI						
at 2 years	118	105	±20	85	106	±17
Stanford-Binet IQ						
at 3 years	107	103	±17	75	105	±21
at 4 years	86	106	±17	68	107	±13
at 5 years	58	106	±14	45	103	±15
WISC-R						
at 6 years	43	110	±12	44	109	±13

It still remains to be determined whether or not subtle neuropsychological disorders or learning difficulties are averted by early treatment of congenital hypothyroidism.

Developmental Neurobiology

Neural Tube Defects (NTD): Neural tube defects (anencephaly, encephalocele, spina bifida) constitute one of the most common congenital abnormalities and are generally accepted to be caused by an interaction between genetic and environmental factors. Preliminary results from the United Kingdom, where the incidence of NTD is higher compared to the U.S., suggest that multivitamin supplementation during pregnancy of women with a history of previous NTD births significantly reduce the recurrence rate of NTD when compared to unsupplemented mothers. Because of the non-random assignment of subjects and controls, the results of the study are open to question especially since the supplemented group included a disproportionate number of women from high socio-economic status.

NICHD is currently supporting a project dealing with the prevention of NTD by folate supplementation prior to and during pregnancy in the golden hamster. This animal model has a 17 percent spontaneous rate of occurence of NTD. Although preliminary results based on a limited number of animals suggest that folate supplementation can reduce the incidence of NTD in this animal model, further studies are required to include a larger number of hamsters.

Prenatal Diagnosis

Chorionic Villi Sampling: Since the safety and accuracy of amniocentesis for the prenatal diagnosis of genetic disorders was demonstrated about ten years ago, many women over 35 years who become pregnant volunteer to have this diagnostic procedure. But this procedure has some drawbacks, among which are the limited amount of fetal cells that can be recovered from

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the amniotic fluid; the lengthy wait before the cells can be analyzed and a diagnosis made; and the procedure cannot be done safely before the 14th week of pregnancy in most cases.

Chorionic villi sampling (CVS) is a diagnostic procedure which can be done as early as the 8th week of pregnancy. After convening a group of scientists who discussed the scientific and ethical issues involved in CVS, NICHD decided to publish a request for grant proposals to determine the safety and accuracy of this procedure compared to amniocentesis. This prospective, randomized trial will involve the cooperative efforts of seven contributing centers and one data coordinating center. The project was initiated on July 1, 1984 and will be conducted as a Cooperative Agreement, the first time this mechanism has been used by NICHD.

Prenatal Diagnosis of Inborn Errors of Metabolism: NICHD-supported investigators have been developing a stable isotope dilution assay for metabolites in amniotic fluid for the early prenatal diagnosis of inherited metabolic disorders. Determination of enzyme activity in cultured amniotic fluid cells for diagnosis requires three to six weeks to culture sufficient cells. Moreover, there are occasional problems such as failure of the cells to grow, contamination of the cells by microorganisms, or contamination by maternal cells. Direct measurement of elevated metabolite levels in the amniotic fluid avoids these problems and can provide a diagnosis in a few days. The investigators believe that the most reliable method for assay of metabolites is by stable isotope dilution in which a known amount of labeled compound is added to the amniotic fluid, the compound isolated and the ratio of unlabeled to labeled compound determined by gas chromatography-mass spectrometry. Assays have already been developed for a number of inborn errors of metabolism. Their accuracy require clinical testing before they can be routinely used for prenatal diagnosis.

BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

Research on Infants at Risk for Mental Retardation

A number of risk factors have been identified as precursors of mental retardation. Scientists in several of the MRRC's have been engaged in basic and applied research on infants who display these characteristics. The most prominent of these risk factors are low birth weight and preterm birth.

Investigators at the Kansas MRRC studied 45 preterm infants who were tested using a variant of the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). Their performance was compared with that of 45 full term infants matched for race, sex, and maternal education. Preterm infants were assessed in the hospital when they were 36 weeks gestational age, at 40 weeks gestational age, and at 4 weeks post discharge. Full term infants were also assessed at 40 weeks gestational age and at 4 weeks of age. Results indicated that the two groups of infants differed on a number of variables derived from the BNBAS at 40 weeks gestational age and at 4 weeks post-discharge. From these data it is evident that parents of premature infants take home babies who behave differently from full term infants. It may be that maternal compensatory

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stimulation in the early weeks and months of life helps to diminish behavioral deficits in preterm infants. However, if such maternal mechanisms are not invoked, the preterm infant's development may be compromised.

The importance of exploration of objects was emphasized by Jean Piaget in his theory of the development of intelligence. One research team at the MRRC at the Albert Einstein College of Medicine has been investigating how preterm infants explore objects when they are 9 months of age. Thirty preterms and 20 full term infants matched for socioeconomic status were compared regarding their exploratory behavior of a standard set of objects. No differences were found between the two groups until the preterms were subdivided according to early medical and neurobehavioral factors into a low risk and high risk group. The high risk group showed significantly less exploratory behavior than either the low risk preterms or the full term. The preterms were administered a developmental test at two years. The correlation between the developmental test and the earlier exploratory assessment revealed a high correlation between the two. Furthermore, it was found that exploration at 9 months was more highly related to imitation and comprehension of language($r=.70$) than it was to eye/hand skills ($r=.43$). These results suggest that manipulative exploration is related to cognitive development either directly or indirectly and that further work along these lines might lead to an instrument which might be used to predict cognitive functioning in early childhood.

Physiological Processes

Persons with Down syndrome suffer more hearing loss than normally developing individuals, and infants with Down syndrome are believed to be at higher risk for peripheral hearing loss. Given this risk for hearing impairment among infants with Down syndrome, audiological testing during infancy is critical to providing appropriate intervention. Communication specialists at the University of Washington's Child Development and Mental Retardation Center recorded the auditory brain-stem responses of infants with Down syndrome. Their responses to click sounds at ages 3, 6 and 12 months were compared with 35 normally developing infants at the same ages. Significant differences were found between the normal and Down syndrome infants. These differences indicate that the latency-intensity curves used to test normally developing infants do not serve as adequate normative values for infants with Down syndrome--particularly at 12 months of age. Results also indicate that the cochlear function of infants with Down syndrome may differ from normal infants by age 12 months.

A research team at the University of Wisconsin MRRC has been working to develop an electrophysiologic profile for the early detection and more accurate categorization of patients with sensory-perceptual and cognitive disorders. Over the past year significant progress has been made in attaining this goal. Several studies have been published indicating the progress toward the goal of establishing an electrophysiological profile which could be used to make definitive diagnoses. These studies provide evidence of purely motor disorders which had been diagnosed as cognitive disorders. In many of the

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cases tested the information obtained from the evoked potential testing could not have been obtained from alternative measures or was produced in a more convenient fashion than was possible by other means.

At another MRRC, researchers have been studying autistic children using EEG methods. These researchers report that early autism may be associated with an atypical pattern of cerebral lateralization. Based on EEG measures of hemispheric activation during cognitive processing it was found that 7 of 10 autistic youngsters tested showed a pattern of hemispheric specialization rarely seen in the normal population. That is, the autistic children were shown to have a "reversal" in lateralization reflective of a lack of left-hemisphere specialization for linguistic functions.

Furthermore the autistic individuals' pattern of cognitive strengths and weakness is suggestive of selective impairment of the left cerebral hemisphere. This does not necessarily mean that the language deficit often associated with autism is caused by this hemispheric deficit. It is possible that both the left hemisphere deficit and the language impairment are caused by a third, as yet unidentified, factor.

Cognition and Learning

A major focus of behavioral research supported by the MRDD Branch has been research on learning and cognition. There is a broad range of studies under this heading from basic research with infants to instructional programs in classroom settings.

Although children born prematurely are believed to be at risk for developmental deficits, these deficits have not generally proven detectable during infancy. In an effort to improve prediction of later cognitive performance and gain an insight into the nature of early aberrant development, infants' visual recognition is being studied by an investigator at the MRRC at Albert Einstein College of Medicine. Six and 12-month old full term and preterm infants were tested with increasing familiarization time. Each infant was given trials in which a shape was viewed for either 10, 15, 20 or 30 seconds and then was tested for visual recognition memory using the paired comparison technique. While older infants showed evidence of recognition memory after shorter familiarization time than the younger ones, at both ages, preterms required considerably longer familiarization times than full term. The pattern of performance replicates earlier findings by the same investigator of developmental lags in the visual information processing of 6-month-old preterms and extends these findings to 12-month-olds. These results suggest that there are persistent differences between preterm and full term infants throughout at least the first year of life in this very fundamental aspect of cognition.

In recent years there has been an explosion in the number of research techniques which have been developed for studying cognitive processes. One investigator supported by the MRDD Branch has proposed to test different parameters of cognitive functioning in mentally retarded persons. This project will test retarded subjects using ten tasks which yield a score

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of information processing variables. The study will examine which of these variables predicts psychometric intelligence. One outcome of this study may be an information processing test battery which may provide more practical information for teaching retarded persons than traditional I.Q. tests. The project will also provide new information about cognitive deficits associated with mental retardation.

Behavioral scientists are constantly challenging old theories and data. A recently supported scientist is examining the assumption that retarded children and adults fail to use rehearsal strategies when trying to memorize some study material. This researcher will examine the question of whether short term memory is defective in retraded persons and also whether rehearsal strategies are employed by retarded individuals.

Other researchers supported by the MRDD Branch continue to study semantic memory (memory for meaning) as well as individual differences in memory among retarded children. Some of these scientists have begun to apply their findings to specific curricula to be employed in schools. It is expected that results from these research programs might also be applied in work and residental programs for retarded persons.

Amelioration and Treatment of Retarded Children

The MRDD Branch supports research programs aimed at treatment of retarded children and any handicapping conditions associated with their disorders. There are a number of different approaches taken including very specific efforts to eliminate self-injurious behavior found among many severely and profoundly retarded children.

Although there can be little doubt as to the short-term efficacy of behavior modification procedures for managing self-injurious responding when properly applied, most often these procedures are implemented in contrived situations and require sophisticated trainers. In addition, long-term follow-up of clients treated for their self-injurious behavior has not produced very encouraging results. This is most often due to changes in the the clients' environments or in other disruptions that interfere with the treatment. One research group at the Vanderbilt University MRRC has recently developed and evaluated new procedures which decreased self-injurious responding in a number of severely retarded adults. These procedures consisted of prescribing a daily jogging program. The experimental intervention led to decreased self-injurious behavior while it was in effect. Following termination of the program, aberrant responding again increased. The investigators are currently studying whether any exercise depresses self-injurious behavior or whether jogging specifically is effective.

Family Processes and Interaction

Behavioral researchers at the University of Washington MRRC compared differences in social competence between premature and full term mother-infant pairs. Consistent with other reports, they found premature babies to be less active, less responsive, to vocalize and smile less, and avert their gaze and bodies more often compared with full term infants. There was also less positive general affective tone among prematurely born babies, with the more

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dramatic differences in 8 month and 12 month interactions with mothers. Social interaction with the mothers differed between the groups throughout the first year. The prematures experienced greater activity and stimulation by their mothers but were less responsive and competent. Furthermore, both members of the dyad with a premature experienced less pleasure and positive affect from their interactions. Given that social and environmental factors may be stronger determinants of outcome than infant birth status, future longitudinal observations will help define the contribution of interactional differences to developmental outcome.

Another research group, this one at the University of Wisconsin MRRC, have developed and refined a measure of mother-infant interaction. This index was developed with the help of recent statistical and computer techniques. The index may be helpful to clinicians who wish to characterize social interactions between mothers and their handicapped infants. These researchers are currently investigating the use of their interaction index in a group of Down syndrome infants. Their initial case studies indicate that although the number of vocalizations emitted by mothers and their Down syndrome infants do not differ from non-delayed infant-mother pairs, the Down syndrome infants and their mothers are less responsive to one another's vocalizations than the non-delayed dyads. These results suggest that specific interventions may be implemented to increase the responsiveness of mothers and their Down syndrome infants. Such efforts may facilitate the language development of the infants.

Children with minor physical anomalies often have behavioral problems and some developmental disorders. A research group at the University of Washington MRRC recently reported the results of an investigation of 152, 4-year-old children for minor physical anomalies. An innovation in the research was that the investigators also examined the adequacy of the home environment for fostering optimal development. They found that children with higher anomaly scores were likely to have poor motor abilities and lower language competence if they lived in less optimal home environments. No reliable associations were found between minor anomalies and developmental measures among children living in relatively well organized and stimulating homes. The investigators concluded that, given the mediating effects of the home environment, minor congenital anomalies are not clinically useful predictors of either development or behavior.

Behavior Disturbance in a Mentally Retarded Population

It is often forgotten that being mentally retarded places great stress upon the retarded person. Such stress usually leads to an internal reaction which generally is expressed as some sort of behavior disturbance. Unfortunately, we do not have very adequate epidemiological data indicating the rates of behavior disturbance among retarded persons.

A group of researchers from the MRRC at the Albert Einstein College of Medicine have examined a 5-year birth cohort of all young adults who had been classified as having been mentally retarded at one time. The birth cohort was all from the same city. A classification of behavior disturbance was developed that was appropriate for the study and used features of the classification recommended by the World Health Organization. Approximately 60 percent of the study population showed evidence of behavior disturbance in

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childhood and in the post-school period from ages 16 to 22. The figure drops to 37 percent when only moderate to severe degrees of behavior disturbance are considered. Hyperactive behavior and aggressive conduct disorder were most frequent among the most severely retarded individuals in the population during the childhood years. Antisocial behavior was most frequent in both childhood and young adulthood for the mildly retarded individuals. Emotional disturbance was more frequent among females in the post-school period, and antisocial behavior was more frequent among males both in childhood and the post-school period. These results provide important baseline information on the rates of behavior disturbance in mentally retarded persons who have been studied longitudinally. This research group is continuing to examine their data for associations with other developmental disabilities and behavior disturbance.

STAFF ACTIVITIES

CONFERENCES

Three scientific conferences were conducted by the MRDD Branch in FY 1984. The conference on "The Intergenerational Effects of Stressors" was held in Bethesda, June, 1984. It addressed the growing research evidence which shows transmittal to successive generations of the preconception effects of protein-calorie malnutrition, certain drugs, and environmental stressors. The conference participants concluded the meeting with a recommendation that the MRDD Branch develop and implement an initiative to stimulate and expand research in this area.

Jointly sponsored by the Branch and the National Institute for Handicapped Research (NIHR), a conference on "The Development of Control, Coordination, and Skill in the Mentally Handicapped" was held in Bethesda, September, 1984. The conference on "Identification of Infants at Risk for Mental Retardation and Developmental Disability" addressed Branch concerns for facilitating research in this area.

AWARDS

The work of Dr. Theodore D. Tjossem, Chief, MRDD Branch was recognized by his being named President Elect, Division 33 (Mental Retardation) of the American Psychological Association, and by award of the President's Citation by the American Association on Mental Deficiency.

PUBLICATIONS

Three new books, the eleventh, twelth and thirteenth, in the Mental Retardation Research Centers Series were produced in FY 1984. All are based on the proceedings of conferences supported by the NICHD. They are:

Environments and Behavior: (Eds.) Kernan, K. T., Begab, M. J., and Edgerton. University Park Press, Baltimore, 1984.

Research Perspectives in Cytogenetics: (Eds.) Sparkes, R.S. and de la Cruz, F.F.. University Park Press, Baltimore, 1984.

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Cognition and Learning in the Mentally Retarded: (Eds.) Brooks, P. H., Sperber, R., and McCauley, C. L. Erlbaum Associates, Hillsdale, N.J., 1984.

"Facts About Down Syndrome," prepared by MRDD staff and the Office of Research Reporting is a new brochure released for distribution in FY 1984.

With the assistance of MRDD staff, the American Journal of Mental Deficiency (AJMD) published a Special Issue detailing the work of the Mental Retardation Research Centers (MRRCs) with a Foreword by Dr. M. B. Lipsett, Director, NICHD. The issue appeared in Volume 88, March, 1984 of the AJMD.

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Human Learning and Behavior Branch (HLB)

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OVERVIEW

The Human Learning and Behavior Branch (HLB) supports basic research and research training on behavioral development from the perinatal period to the beginning of adulthood. To attain the goals of this mission the Branch employs a variety of support mechanisms. These include regular research grants, program projects, institutional training grants, individual postdoctoral fellowships, research career development awards and contracts. The research knowledge gained provides a basis for understanding the ontogeny of normal development and criteria for assessing developmental delays and learning disabilities.

The primary focus of the Branch's program is to develop and support research which promotes children's health. This is accomplished by funding research grants which in the aggregate are designed to determine how the interaction of biological, psychological, and socioenvironmental factors result in normative behavioral development and to identify those factors which interfere with such development. Processes and behaviors specific to each stage of development are investigated. These include studies of behavioral development in children born at biological risk for a variety of behavioral disabilities: learning problems, delayed or impaired speech, and dyslexia. Biological, behavioral and social science disciplines all play key roles in achieving the Branch's mission.

PROGRAM ACTIVITIES

FINANCIAL SUPPORT

During the time covered by this report, funds for the five program elements amounted to $16,006 million. Of the total 166 grants supported, approximately 80 percent (130) are regular research grants. Such grants are provided to individual investigators who initiate the ideas and foci for their research projects. A full breakdown of financial support is provided in Table 4. The Branch also supported seven program projects. Such grants are made up of at least three subprojects all of which relate to a central research theme on the topic of behavioral development. The results from some of these projects are provided in the research highlights.

RESEARCH TRAINING

Training of predoctoral and postdoctoral researchers is an integral part of the Branch mission. This is carried out through the award of institutional training grants and individual postdoctoral fellowships. During the time covered by this report support of training amounted to $1.3 million.

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Table 4.

NICHD GRANTS AND CONTRACTS ACTIVE DURING JUNE 1984
HUMAN LEARNING AND BEHAVIOR BRANCH

Funds (in thousands)

Health Area	Total		Research Grants								National Research Service Awards		Research Contracts	
			Total Research		Research Projects		Program Projects		RCP Awards					
	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds	No.	Funds
Total	166	$16,006	144	$14,763	130	$11,232	7	$3,257	7	$273	21	$1,034	1	$209
Developmental Behavioral Biology	49	4,035	41	3,892	37	3,563	1	211	3	117	8	143	-	-
Human Learning, Cognition, Perception, Memory	42	3,714	33	2,947	28	1,870	2	957	3	120	9	767	-	-
Social and Affective Development	24	2,052	24	2,052	24	2,052	-	-	-	-	-	-	-	-
Human Communicative Processes	33	4,315	28	3,982	24	1,893	4	2,089	-	-	4	123	1	209
Behavioral Pediatrics	18	1,891	18	1,891	17	1,854	-	-	1	36	-	-	-	-

NOTE: Excludes the scientific evaluation grant.

NICHD-OPE-PAS
July 18, 1984

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RESEARCH HIGHLIGHTS

The program is divided into five major elements: (1) Behavioral pediatrics, (2) Biological bases of behavioral development, (3) Learning and cognitive development, (4) Communicative abilities; and (5) Social and affective development.

Research in behavioral pediatrics focuses on applying principles of human learning to health and illness behaviors of children. In some cases adults significant in a child's environment are studied to gain an understanding of which behavioral mechanisms are instrumental in promotion of health and in prevention of disease. The goals of this element are: (1) To link the basic findings in behavioral development with clinical concerns associated with the practice of pediatric medicine, (2) to determine how children learn about health and react to illness, (3) to examine the developing behaviors which promote health and well-being across the age span, (4) to study how lifestyles develop which encourage risk taking, and (5) to examine how these factors contribute to the etiology and onset of disease and impact upon the public health.

Included in biological bases of behavioral development are studies of brain/behavior relationships, the biochemical, physiological and hormonal bases of behavior, sensory motor processes, and comparative animal behavior. This program element is divided into six topic areas: (a) Developmental behavioral neurobiology, (b) Developmental behavior genetics, (c) Developmental behavioral endocrinology, (d) Developmental behavioral pharmacology, (e) Sensory and psychomotor development, (f) and Comparative animal models of behavioral development.

Learning and cognitive development includes research on basic learning mechanisms which are necessary for optimal behavioral development. In addition, support is provided for studies of perception, cognition and memory. While the emphasis has been on infants, research applications are also encouraged for studies of children and adolescents.

Communicative abilities research includes studies on the acquisition and development of speech, language, and reading ability in children. Included are studies of basic mechanisms, both physiological and behavioral, which underlie language and the learning of language by children. Special emphasis is given to research on the neural, genetic, and behavioral factors involved in dyslexia

Research in social and affective development is designed to gain an understanding of the basic behavioral, psychological, and genetic mechanisms involved in normal social and emotional development. Included are studies of temperament, the family as a context for social and emotional development, prosocial behavior, development of self and body image in adolescents, and the influence of endocrines on emotional development. Also covered under this rubric are experimental studies which employ comparative animal models of social and affective development.

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BEHAVIORAL PEDIATRICS

Neonatal Behavior

Grouped in this category are basic research findings which have implications for the clinical practice of pediatrics. Three studies underway are now investigating neonatal sucking, measurement of hearing in one-day-old babies, and the psychophysiology of pain development.

A Branch supported investigator has developed a computer simulation program to analyze sucking behavior of human neonates. This work has great potential for assessing the functional integrity of the central nervous system, adaptive behavior, and specific feeding skills. Ultimately this computer system may provide the basis for teaching more efficient sucking in at-risk infants who have deficient or immature sucking response patterns.

Further progress has been made on studies designed to assess behavioral and adrenocortical responses to stressors in neonates. The investigators found that cortisol levels reached similar elevations in response to respectively the Gomco Clamp and the Plastibell procedures for circumcision. By 150 minutes postprocedure all neonates had their cortisol levels returned to precircumcision levels. This demonstrates a somewhat unexpected result, namely the similarity of clearance rates for neonates and adults.

In addition, the investigators have developed a new method for measuring cortisol levels which uses a saliva sampling technique. Preliminary results suggest that the saliva-cortisol procedure is as sensitive as the plasma cortisol assay.

Work is continuing on the development of using the eyeblink for measuring hearing in the one-day-old neonate. Studies during this past year have focused upon parametric analyses of the startle reflex. The investigators have also modified their equipment to provide a more objective measurement of the eyeblink amplitude by using a miniature photodensitometer instead of an observer's subjective rating.

One difference between infants and adults was that a tone prior to a tap inhibited the eyeblink in adults but not in babies. The neonates showed reflex augmentation to both intensities of tones studied (70 and 90 db) but did not show inhibition with either.

Studies of the parameters necessary for obtaining reliable and robust reflex augmentation in neonates revealed that an optimal response may be obtained using a 1 KHz tone with binaural presentation. These findings provide added optimism that reflex augmentation can provide objective and reliable assessment of hearing in neonates.

Health Behavior

A study currently supported by NICHD is attempting to teach third and fourth grade elementary school children how to deal with pain. The program focuses upon recognizing pain's defensive signal function, developing coping strategies, and recognizing and avoiding the use of pain behaviors for secondary gain. Within a small group format, direct teaching, symbolic modeling, role play, discussion and

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debate are employed to teach an understanding of pain issues and develop cognitive coping strategies.

Illness Behavior

To assess the long-term impact of childhood disability on both the children and their families, an NICHD grantee is following up families of children with cystic fibrosis, cerebral palsy, myelodysplasia and multiple physical handicaps, and a comparison group of randomly selected families with children from the same community. The consequences of the child's physical disability are examined in terms of the child's adjustment (psychological, physical and school) and the functioning of the family, including parents and the normal siblings. Current findings appear in two reports. In a forthcoming issue of the Journal of Abnormal Child Psychology, Naomi Breslau and Iris Ann Marshall have reported on a five-year follow-up of psychological disturbance in children with physical disabilities. The major finding was that children with conditions involving brain abnormality who had been classified initially as severely disabled remained at this level five years later. Children with cystic fibrosis, however, who had been classified as severely disturbed, improved over time.

A second study found that mothers of disabled children checked off a high rate (30 percent) of depressive symptoms on a widely used self-report measure, but their actual rates of depressive (current, life time or past six months) did not differ from the rate for women in the general population. These mothers also showed higher rates of generalized anxiety than in the general population.

Children's physiological response to stress is the subject of two new studies. In one study, the investigator is examining how children 6 to 10 years of age cope with the medical and hospital procedures associated with tonsillectomies or adenoidectomies. The main purpose of this research is to determine whether these children, like hospitalized adults, use different styles of coping. Multiple biological and behavioral data will be collected from standardized interviews of coping styles, videotaping of play behavior, monitoring of activity level and heart rate, time lapse videotaping of nighttime sleep and urine assays of cortisol, norepinephrine and epinephrine--measures affected by stress.

Another NICHD-supported investigator is examining pubertal change as a period of stress for adolescent girls. Specifically, the study focuses upon the relationship of pubertal status, especially delayed and asynchronous puberty, to psychological functioning. Two groups of adolescent girls are being followed longitudinally for four years: one group, known to be at risk for delayed puberty and asynchronies in physical development, is composed of girls in a professional ballet school; the other group consists of girls from comparable demographic backgrounds. The findings from this study will be useful in identifying the psychosocial precursors of eating disorders in girls, particularly anorexia nervosa and bulemia.

Risk Taking Behavior

Research sponsored by the NICHD is focusing upon gaining an understanding of the processes by which children become cigarette smokers.

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One Branch supported study is developing fine grain measures of smoking topography in adolescent cigarette smokers comparable to those which have been collected in adults. Forty-six adolescents who are current smokers were videotaped in pairs in a laboratory situation. The children were advised that they did not have to smoke but if they chose to do so, were required to use an automatic cigarette holder. This apparatus allowed the researchers to accurately measure puffs per cigarette, puff duration, and integrated puff pressure. Measures of expired carbon dioxide were obtained prior to smoking and after every cigarette. It should be added that subjects were counseled about the dangers of smoking and have been advised on ways to stop.

Preliminary results indicate that there is a good correlation on the same measures of smoking topography from cigarette to cigarette. Another preliminary finding is that when the rate of cigarettes smoked is controlled for, the amount of carbon dioxide is greater for adolescents who have had a longer history of smoking. This implies that more experienced smokers may take more puffs or have a greater depth of inhalation than less experienced smokers.

The results of this study are important because if topography measures are reliable and can be calibrated against objective biochemical measures of exposure levels, researchers can noninvasively estimate dosing levels and smoking experience during field observations of children who are smoking in their natural environments.

BIOLOGICAL BASES OF BEHAVIORAL DEVELOPMENT

Developmental Behavioral Neurobiology

Work in this area is focused upon brain/behavior relationships and how environmental conditions can influence both brain and behavioral development. One study still underway is investigating the affects of rearing conditions on behavioral competency and brain sexual dimorphism. Male and female rats raised for 30 days (postweaning) in either a complex or isolated environment were examined for potential differences in brain anatomy. The results of the study reveal that females raised in complex environments have more dendritic material in their dentate gyrus of the hippocampus than females raised in isolated environments. Males on the other hand showed no difference in the same anatomical locus.

Studies by this same investigator illustrate that differential rearing effects behavioral performance. Rats were raised for a month postweaning in either complex or isolated environments. They were then tested in a 17 arm radial maze. Those rats raised in the complex environment showed superior learning performance (number correct, number of errors, etc.) over those raised in isolated environments. Such findings are not unusual since they have been previously demonstrated. What is interesting is the fact that there were no significant sex difference or sex by environment interactions.

Another of our Branch-supported researchers is studying relationships between limbic system function and behavioral development in rats. The work is based upon the observation that the septo-hippocampal portion of the limbic system

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undergoes a rapid rate of development during the 10 to 25-day age range postnatally. These brain changes are being related to the behavioral development of the rat pups during the same age range. Questions of interest include issues of brain plasticity. For example, if lesions are made in the septo-hippocampal system, is emerging behavior impaired and does it recover later in development? The behavior of interest focuses upon reward scheduled effects that are termed "paradoxical" in adult animals. Specific behaviors are single patterned alteration (first appears at 11 days postnatal); partial reinforcement extinction (first appears at 12 to 14 days). Results from one study show that lesions of the hippocampus in 10 to 11 day old rats do not eliminate single or patterned alternation at 16 days of age or in adults. However, the same lesion eliminates the partial reinforcement extinction in behavior at both ages (16 days old and in adults). This work is significant because it shows how specific subsystems are necessary for particular behaviors to be acquired and sustained.

Developmental Behavior Genetics

Branch supported scientists are attempting to assess genetic and environmental influences on human behavioral development. Scientists have found that some traits, such as individual differences in language acquisition show substantial genetic influence and little family environmental influence; other traits, including Bayley Mental Scale scores, show moderate genetic influence and moderate family environmental influence; still other traits, including handedness, display neither genetic nor family environmental influence. In an analysis of other data from the same study it was found that the correlation between the genetically determined portion of verbal and nonverbal ability, while near unity at birth, decreases to some extent by age two.

The physical and mental growth of twins has held the interest of scientists for many years. One investigator has followed the long-term consequences of prenatal growth suppression in twins for several decades. His studies of twins are of particular significance because twins are often premature and have lower than expected birth weights. The results of this research show that the initial deficit in weight found in twins is progressively offset during childhood. However, low birth weight identical twins continued to have a small residual weight deficit even at age six. Height, while initially suppressed, appeared to be unaffected when measured at age six. The initial depression in scores on tests of mental ability was recovered by age six for most twins. Low birth weight infants of mothers who were from lower socioeconomic status groups continued to show a significant decrement in mental abilities at age six. This may be explained by the finding that the education level attained by these mothers was low and the lower scores of their children may be a reflection of their genetic predisposition for low intelligence rather than low birth weight.

Developmental Behavioral Endocrinology

The Branch supports a number of projects designed to assess the relative roles of hormones and social/environmental factors in the development of sexual and nonreproductive behaviors. Preliminary data from one such study of primates (Japanese macaques) suggest that prenatal hormones can masculinize play behavior and influence the dyadic interactions between mothers and their offspring. The investigators implanted 20 multiparous females with crystalline testosterone.

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The monkeys were then reinstated into their natural troops and 60 days later the implant was removed. These females produced a total of eight infants (four females [hermaphrodites] and four males). The infants and their mothers were observed three times every two weeks over a period of three months. Results indicate that the males played significantly more than the females. Hermaphrodites played more than females, but the differences were not significant. Another finding of interest was a nonsignificant trend for mothers of male infants to break contact with their offspring more than did mothers of hermaphrodites. Mothers of hermaphrodites also exhibited a nonsignificant trend to break contact with their infants more than did mothers of female monkeys.

Another study which employs songbirds as subjects is investigating the roles of androgens and estrogens in the expression of species-specific song and social behavior. Preliminary data suggest that estrogen is necessary for the activation of courtship singing in male zebra finches. While androgen has also been demonstrated to be necessary for expression of male song its sites of action are both peripheral and in the brain. Estrogen on the other hand acts only within the brain. Of interest also is the finding that hormonal control of a particular behavior is not invariant. The data reveal that singing in the context of courtship is influenced by metabolites of androgens and estrogens. However, singing used in the context of aggressive display does not appear to be hormone dependent. Castrated male birds sang to a male intruder but not to a female.

Work focused upon the elucidation of prenatal hormonal influences upon behavioral development in humans involves the study of people who were exposed in utero to endocrines given to their mothers in connection with pregnancy. One project has been studying the long term affect of prenatal hormones by evaluating the birth registries of a cohort of Danish people whose mothers took one of three progestins. The results presented are based upon preliminary analysis of data obtained from a subsample of 315 from the 1959 to 1961 Danish Perinatal Cohort. The preliminary data analysis suggests that performance of hormone-exposed subjects in comparison to matched controls varies as a function of hormonal substance and sex. Measures included in the test battery used do discriminate between exposed and nonexposed subjects in terms of sexually dimorphic cognitive and personality variables. On mental ability tests, progestin exposed males made more errors on acquisition and retention phases of word pairs. Similarly, progesterone exposed males achieved lower scores on both an identical pictures test and a card rotation test. Females exposed to synthetic progestin performed less well on a Gestalt completion test. On personality measures, females exposed to progesterone were more work-oriented than controls, and were more likely to report approaching rather than avoiding novel stimuli. Females exposed to synthetic progestin were less work oriented than controls, showed more masculine traits, were more conscientious and persistent, more restrained, more trusting and accepting of conditions, and were more obedient (accommodating, submissive) than controls. Males exposed to corticosteriods during gestation showed more positively valued masculine traits and fewer negatively valued communal traits. Progesterone-exposed males are more distractable, less rhythmic, and have a more positive mood than matched controls. The Leifer-Roberts Response Hierarchy Test could distinguish between prenatally exposed (progestins) and nonexposed, same-sex siblings.

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Developmental Behavioral Pharmacology

Work in this domain is designed to evaluate the effects of drugs on the developing organism. One Branch supported project is studying the effects of caffeine upon behavioral development in rabbits. These organisms were chosen because they metabolize caffeine similar to the way people do. Starting with birth, the offspring of caffeine-treated and control rabbits were placed on activity platforms. New data analysis procedures allow the recorded movement patterns to be analyzed into sleep/wake cycles. The data are now being analyzed to determine the affects of caffeine on these state variables. This work is important because it is the first systematic study of caffeine's effects upon behavioral development.

LEARNING AND COGNITIVE DEVELOPMENT

Early Learning in Animals

Two Branch supported researchers are studying prenatal learning. One scientist who has been studying imprinting in mallard ducklings has reported the discovery of an *in ovo* cortical period for learning the maternal call. His results indicate that when the mallard duck embryo is stimulated by the species-specific maternal call while still in the egg, it will show a preference for that call postnatally. If developing ducklings are not exposed to the maternal call *in ovo* but receive such stimulation just after birth, they do not exhibit a preference for the maternal call at the normal postnatal age. This finding represents the first example of an embryonic critical period that is necessary for postnatal behavioral adaptation.

Another Branch supported researcher is studying *in utero* learning in fetal rat pups. As reported in last year's overview of progress, he demonstrated that by using an aversive learning paradigm fetal rat pups could be conditioned *in utero* and the learning was retained postnatally. During the past year he has extended his findings and demonstrated that 17-day-old rat fetuses can be conditioned *in utero* and and they consolidate this learning on day 19 of gestation. In this study, with the mothers under light anesthesia, 17-day-old rat fetuses were exposed *in utero* to a novel stimulus (mint), followed by an interperitoneal injection of lithium chloride. Using a chemomyelotomy preparation, the female rat was placed into a warm saline bath for observation on day 19. Subject fetuses were then re-exposed to the mint stimulus and observed for 10 minutes. Significant behavioral differences were found between fetuses that had received lithium chloride versus saline (controls) on day 17. The lithium chloride treated fetuses showed less activity, fewer complex movements, fewer hindlimb movements, and more whole body curls and stretches than the saline controls. These data indicate the ability of 17-day-old fetuses to form associations and respond to conditioned stimuli prenatally. In another Branch sponsored project rat pups between 3 and 9 days of age are being studied to determine their response to artificial odors in the dam's diet. They have demonstrated that an odor (eucalyptol) added to the diet of the mother during pregnancy and lactation elicited vigorous probing and behavioral activation in her pups especially between 3 and 9 days of age. The odor of eucalyptol also enhanced intake of water infused into 6- and 9-day olds. They also found that raising pups in a eucalyptol scented environment (without treating the dam's diet) was not

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sufficient to produce the findings reported. Pups were also tested for eucalyptol scented versus unscented bedding. The unscented bedding was preferred by normally reared pups whereas the eucalyptol scented bedding was overwhelmingly preferred by pups whose dams were fed a eucalyptol-treated diet. Pups merely exposed to eucalyptol odor during rearing showed no preference for either bedding. Such findings are important in that they demonstrate that aspects of the pups' ingestive behavior can come to be elicited by arbitrary odor cues in the dam's diet, perhaps in the same way that these components (activation and probing) come to be elicited by odors predicting milk infusions in the more traditional classical conditioning paradigm.

Early Learning in Human Babies

A newly funded Branch supported scientist has demonstrated classical conditioning in human babies during the first day of life. Heretofore, studies attempting to demonstrate classical conditioning early in the life of human babies have been severely criticized on methodological grounds. Therefore, the literature on this topic has been dismissed by most developmentalists who have taken the position that classical conditioning has not been demonstrated to occur early in life and have concluded that it is not an important learning mechanism in the natural ecology.

While the Branch supported research is only just in its beginning stages, the findings are quite significant from both a theoretical and clinical viewpoint since the data contradict the prevailing viewpoint. Should the replication and expansion of these proposed studies prove to be reliable phenomena, this will lead to a reexamination of classical conditioning's role in early behavioral development in human neonates.

Infancy

One Branch supported grantee has been studying auditory perception in infants. Using a head turning procedure (babies were reinforced for turning their head when the frequency of the auditory stimulus changed) he investigated the auditory frequency discrimination capacity of 7- to 9-month-old infants. His findings indicate that babies in this age range are four times less sensitive to frequency differences than are adults.

Researchers sponsored by the Branch have uncovered evidence for intermodal perception. As reported in Child Development the investigators found that 12-month-old babies detect intermodal invariants in substances and perceive the "affordances" (the potential usage or qualities) of the substances. The babies who were familiarized in the dark with either a hard or elastic (spongy) object were then tested for their knowledge about the quality of the objects which they had not seen. They were allowed to view simultaneous films of the objects they had previously handled. One object was moved in the pattern of a rigid object and the other as an elastic object. Infants handled the two substances differently and looked preferentially (first and longer) at the object in the film with which they previously had tactual experience. In effect they were able to appropriately visually identify the properties of elasticity that they had previously only felt.

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COMMUNICATIVE ABILITIES

This aspect of the Branch program focuses upon biological, behavioral and psychological bases of language, speech, and reading development. Work includes research utilizing animals and children to study the development of simple and complex communication behaviors.

Comparative Animal Models

Several researchers have used nonhuman primates as models for understanding the origins and development of language. Numerous studies have demonstrated that the great apes can learn to use a set of symbols or signs to communicate their needs through learning direct relationships between a specific object and a symbol. However, controversy remains over the extent to which apes can use these symbols to communicate as a language. One group of NICHD-supported scientists developed several new procedures for teaching chimpanzees some of the more complex uses of symbols. After several years of training, these chimpanzees learned to use symbols to request missing objects, to refer to categories of needs (i.e. liquids and food), to describe novel events (fright), and to listen for information communicated by symbols by another chimpanzee. These procedures are being successfully applied to the communication problems of severely and profoundly retarded children.

A five-year study of the acquisition of pidgin Sign English by an orangutan found that he used signs at about the same level as a two-year-old human. He uses approximately 100 signs, often in multi-sign sequences, to communicate his needs to his caretakers. An analysis of the orangutan's use of signs revealed that he uses signs spontaneously, self-initiates signing, occasionally adds new information and often uses the context of the situation to order the sequence of signs used to communicate his needs to his caretakers.

Language

During the first six years of life, children are actively engaged in the learning of their first language. Successful acquisition of the rules of language is important to the child's intellectual and academic development. One investigator is studying th trategies used by children learning languages which differ greatly in their structure. Within each of the languages studied (English, German, French, Hungarian, and Serbo-Croatian) some structural rules are cued reliably and frequently. By setting low and high frequency cues into competition with each other, scientists have found that the higher the frequency and greater the reliability of the cue, the more rapidly children learn those rules of the language. These findings could be applied to study errors in adult sentence processing, to improve the acquisition of second languages, and to analyze the decay of language in aphasia.

A study of the American Sign Language (ASL), found that there are primary linguistic systems, passed down from one generation of deaf people to the next, which have been forged into autonomous languages, not derived from spoken language. In order to study the important temporal components of ASL, a group of scientists developed a computer program which allows the manipulation of movement quality independent of spatial path. The synthesized signs were built up into

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complex stimuli and sequenced in real time. A major discovery from this laboratory is that ASL has developed elaborate morphological devices for a wide variety of semantic distinctions. They found that ASL has a large set of grammatical markers that function as inflectional and derivational morphemes-regular changes in the form of signs resulting in systematic changes in meaning. The importance of this work is that the building blocks of a visual-gestural language can be experimentally manipulated and the results can be compared to the grammar of spoken languages and to hemispheric specialization for sign and speech based languages. Right-handers consistently used their right hands to sign, while left-handers used their left hand. This study and others by this group of scientists show left hemisphere specialization for sign language in right-hand signers much like the hemispheric dominance for speech based languages in normal hearing subjects.

Speech

Recent work in this field has questioned the biological specificity of auditory receptors for categorical perception of speech. By manipulating the expectations or the attention of the listener, one experimenter found that he could change the perception of sound from a speech to a nonspeech signal. Another study demonstrated the complex interaction involved between the auditory signal and the visual signal in determining the perceived meaning of an informational unit. He paired an auditory stimulus [ba] with the visual stimulus of a speaker articulating a slightly different sound [vi] and found that the subject's perception was a combination of the auditory and visual signals [va]. These studies are important in improving our understanding of how the perceptual unit is formed.

Reading

The Branch supports numerous investigators who study the reading process. The topics of investigation in this field include examinations of good and poor readers, descriptions of the reading process of skilled, college aged readers, and electrophysiological studies of children at risk for learning disability.

A series of studies by a group of NICHD-supported scientists compared elementary school children who were good and poor readers. They found that poor readers produce more errors than good readers when the task involved listening to speech in noise. Poor readers use a phonetic code but have difficulty retaining the temporal order of a series of phonetic stimuli. The processing strategies for phonetic representations used by poor readers are often immature. Words with one or more irregularities were more often misspelled by poor readers. The pattern of these results suggests that poor readers are less attuned to the phonetic features of the spoken word than are good readers.

One NICHD-sponsored scientist has studied language processing during reading by examining eye movement patterns of students while they read. This investigator has found that the perceptual span of the foveal focus for readers of English is four characters to the left and up to 15 characters to the right of the fixation point. Thus, the fixation point varies as a function of the direction of reading.

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For many years scientists have attempted to use measures of the electrophysiological activity of the brain to predict, diagnosis, and track the course of learning disabilities. The NICHD has supported the work of a scientist who developed a computerized integration of several measures of central nervous system electrophysiological activity which he calls the BEAM EEG. The investigators measured two hundred preschool boys half of whom were suspected of being at risk for having learning disabilities. Several of the children displayed the BEAM EEG patterns generally associated with epilepsy. Yet, only two of these children showed the clinical symptomatology of epilepsy. This finding supports the hypothesized relationship between children at risk for learning disability and epilepsy.

SOCIAL AND AFFECTIVE DEVELOPMENT

Infancy

Work on the development of temperament during infancy is being supported by the Branch. In one such study the investigator has been looking at major dimensions of temperament variation and has examined the coherence of the factorial structure obtained on one cohort of children using a cross validation sample. The findings have led to the identification of three dimensions of temperament. These have been labelled respectively as: (a) negative arousal, (b) fearfulness, and (c) happy-active.

Results from a recently completed study indicate 2- to 3-month-old infants who experienced ample and regular vocalization and social stimulation from their mothers vocalized significantly more to their mothers than to a stranger. In contrast, those infants who received only minimal interaction did not exhibit differential vocal responsiveness (DVR) to mothers vs. strangers. A curvilinear relationship was found to exist at the extremes of maternal stimulation. High and low levels of maternal stimulation are both associated with lower infant DVR. This implies that excessive stimulation may not optimize vocal responsivity in infants.

Results from another study call into question previous findings that infants at 3 to 4 months can detect emotions from photographs of adults. Based on current findings, infants at 7 months do not detect emotional expressions in still photographs. However, at that age they can discriminate expressions of happiness, anger, and sadness in animated displays.

The ability of infants to perceive affective expression from multimodal signals (i.e., seeing a filmed expression as well as hearing it) is the focus of another NICHD-supported grant. Preliminary findings indicate that 7-month but not 5-month-old infants respond to visual and acoustic presentations that are concordant (invariant), for both angry and happy affective expressions, even when the lower third of each face is hidden from view to prevent infants from simply matching the synchrony of lip movements to the voice.

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Children and Adolescents

Studies of children's social development in the context of play behavior is being investigated by a Branch sponsored researcher. She subjected observational scores of play behavior to statistical analysis in three groups of children (33-months, nursery school, first grade). Based upon the cluster and principal components analysis a major "sociability" dimension was derived which had the same factorial composition at the three ages studied. A second dimension identified indicates the degree to which a child's social behavior is sex typed (involving same-sex versus mixed sex or opposite sex social groupings). The data suggest a tendency for children to choose same-sex partners in their social interactions. This was found to be consistent across cohorts and ages studied.

Children's social adjustment to school transitions (entering elementary or junior high school) is the subject of two ongoing NICHD studies. One project is tracking 750 children from 20 schools through the first two years to see how children's cognitive and social-emotional development are affected by such "proximal" factors as teachers', peers' and parents' expectations as well as the more "distal" factors of race and socioeconomic status (SES). Preliminary findings indicate parents of girls in the first grade rated their children higher than parents of boys in ability to do schoolwork. Black children were rated higher by their parents in ability to do schoolwork compared to white children even though Black children received lower first grade marks than whites. Teachers gave girls better marks in conduct than boys. They also graded white children higher in conduct, reading, and math than Blacks. Parents' initial expectations for their children far outweighted children's expectations for their own grades. Parents of children who failed first grade believed that their children had more ability than their classmates to do the classwork. This was the case despite the fact that these children had lower scores on standardized tests than their classmates at the beginning of first grade.

Another school based study just beginning is examining how the transition from elementary school to middle school (6th grade) or junior high (7th grade) affects children's achievement, self concept, and motivation in math and science. The overall hypothesis is that the commonly observed decline in achievement motivation at this age is due to changing school environments rather than an effect of early adolescent age shifts. A further prediction is that middle school and junior high school students will show similar transition effects.

Families

Several new studies are examining the interrelationships of family members. One such project is investigating transitions from marriage to parenthood and its impact on the infants' development in the first year of life. Another grantee is studying how families contribute to the competence, career choices and peer friendship patterns of their adolescent children. A third project is exploring the family process variables that either enhance or retard the adolescent's psychosocial development.

The qualitative features of sibling relationships in middle childhood is the focus of an ongoing study using both self-reports (of children and parents) and behavioral interactions between siblings. Analysis of one self-report inventory,

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the Sibling Relationship Questionnaire (SRQ) yielded four factors: warmth/-closeness, relative power/status, conflict, and rivalry. The results suggest that the first three factors are similar to those found in research on other relationships, whereas the fourth factor (rivalry) may be unique to sibling relationships. Furthermore, children reported stronger feelings of warmth/-closeness toward same-sex siblings than toward opposite sex siblings, particularly when the children were close in age. At the same time, children reported more conflict when the age spacing was small than when it was large.

Developmental changes in siblings relationships have also been examined. In general, perceptions of relative status/power did not change very much. The one exception to this generalization was that girls with younger siblings reported an increased differentiation in status. That is, as they grew older girls reported more nurturance and more dominance toward younger siblings, a finding that suggests they have acquired the role of surrogate caretaker. Developmental decreases in conflict were also found for most sibling constellations. These two findings suggest that as children get older and develop a life outside the family, sibling relationships may tend to decrease in intensity.

STAFF ACTIVITIES

WORKSHOPS AND CONFERENCES

The HLB Branch sponsored two workshops and one conference during FY 84. These were: (a) In Utero Learning Workshop (April 30 - May 1, 1984); (b) Men's Transitions to Parenthood (May 31 - June 1, 1984); and (c) Biobehavioral Measures of Dyslexia (September 10 - 12, 1984). An overview of the in utero learning workshop was published in Science (V 225, pp. 302-303, July 1984).

MEETINGS AND PUBLICATIONS

Branch staff have been actively involved in organizing symposia at scientific meetings and publishing research monographs. Dr. Josephine Arasteh organized a symposium at the Society of Behavioral Medicine on Smoking During Pregnancy: Impact on Maternal and Child Health. Dr. David Gray gave an invited talk at the Annual Meeting of the Behavior Genetics Association. It was entitled "Behavior Genetics Research Supported by the Human Learning and Behavior Branch." Dr. Norman Krasnegor is senior editor of two books which are now in press. These are: Developmental Behavior Pharmacology (Erlbaum Press) and Children's Health Behavior: A Behavioral Pediatrics Perspective (Wiley).

STAFF CHANGES

Dr. Phyllis Berman and Mr. Gary Carter (assistant to Dr. Gray) left the Branch. Dr. Gray's new assistant is Miss Victoria Bolton.

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